BRAIN

A JOURNAL OF NEUROLOGY

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A Journal of Neurology

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MARCH, 1937

BRAIN.

PART 1, VOL. 60.

CONDITIONED RESPONSES TO LIGHT IN MONKEYS AFTER REMOVAL OF THE OCCIPITAL LOBES.[1]

BY DONALD G. MARQUIS (YALE UNIVERSITY) AND ERNEST R. HILGARD (STANFORD UNIVERSITY).

SINCE the experiments of Munk (1890) and Brown and Schäfer (1888) it has been accepted that complete removal of both occipital lobes renders a monkey totally and permanently blind. Schäfer was able to demonstrate that the partial recovery of vision which had been observed by Luciani (1884), Ferrier and Yeo (1884), and Horsley and Schäfer (1887) was the result of an incomplete removal of the occipital lobes. Subsequent studies have shown that the essential cortical region is coextensive with the anatomical area striata (Poliak, 1932).

The tests of visual perception used in these studies were observational in nature. It was noted that, when moving about, the monkey bumped into walls and objects in its path. It was unable to locate food placed on the floor except by persistent exploration with its hands. It did not blink or make any other response to threatening gestures. The only reflex response which could be elicited by a bright light was pupillary constriction.

The question of a residual light sensitivity was raised, however, by Brown and Schäfer who wrote, in discussing the performance of a monkey after bilateral removal of the occipital lobes: "Although absolutely unable to see ordinary objects or to form any appreciation regarding them by aid of the visual sense, it is not quite easy to decide whether he is able to distinguish between light and darkness; for, when a large object, such as a tray, is held between him and the light, he will sometimes put up his hand as if to touch it. He does not, however, always respond in this way, and it is possible that the object may be appreciated by other senses than that of sight; for when a strong light

[1] From the Laboratories of Psychology, Physiology, and Neuroanatomy, Yale University.

is suddenly flashed upon him his attention is not diverted towards it" (1888, p. 316).

The conditioned reflex technique offers a method by which any residual light sensitivity can be examined quantitatively. In the present experiments visual conditioned responses have been studied in a series of monkeys before and after bilateral removal of the occipital lobes.

METHODS.

Of the six monkeys used in these experiments, five were rhesus monkeys (*Macaca mulatta*) and one (OP 3) was a spider monkey (*Ateles ater*). Because the procedures were so nearly identical for all animals, individual protocols are not presented.

The operations were performed with full asepsis under deep general anæsthesia induced by sodium amytal. The occipital lobes were removed in two stages, with an interval of two to four weeks elapsing between the two operations. Since the primary purpose was to remove the area striata completely, radical extirpation of the entire occipital lobe was carried out. A large unilateral bone flap was turned down to expose almost the entire hemisphere. After the veins from the occipital cortex had been coagulated with the Davis-Bovie electrosurgical unit, the pia over the simian sulcus was gently incised with the cutting current. The sulcus was dissected to its depth with a blunt spatula and the ablation continued by gentle dissection with the spatula. On the medial surface of the hemisphere the line of transection was extended forward to the splenium of the corpus callosum, the lateral ventricle being opened at about the junction of the temporal and occipital horns. The occipital lobe was thus removed in one block, on which it was possible to identify the entire extent of the calcarine fissure.

Nothing in addition to the routine post-operative care of the animals was found necessary, for even after the second operation they would feed themselves adequately if food was left in the cage. A slight transient hemiparesis was noted after a few of the operations, but no permanent symptoms, other than visual, were observed.

The animals were studied for periods of seven to eighteen months following operation. At the conclusion of each experiment the animal was killed with ether and the brain fixed in situ by perfusion with neutral formalin. After hardening the brain was removed, weighed, and photographed, and the extent of the operative removal determined macroscopically. Sections through the margin of the lesion were stained with thionin for cytoarchitectonic study. Serial sections through the lateral geniculate body were prepared from two of the brains and stained with thionin for cell study.

The technique of conditioning used in this investigation has been described in detail in previous papers (Hilgard and Marquis, 1935, 1936). Conditioned eyelid closing to the noiseless exposure of a light was established on the basis of the unconditioned corneal reflex elicited by a brisk puff of air delivered

automatically to one eye. The movements of the lids were recorded with the Dodge pendulum photochronograph. Artificial paper eyelashes, glued to the margin of the upper lid, projected into the beam of a Pointolite lamp, and the shadows were registered on film carried by the pendulum past a vertical camera slit. Specimen records are presented in fig. 3. Before training, there were no reflex responses to the light stimulus except an occasional lid opening. The interval between the exposure of the light and the succeeding air-puff was 400 ms., and the conditioned response appeared, after suitable training, as a lid closure following the light at a latency of approximately 200 ms. A daily conditioning session consisted of fifty paired stimulations, preceded and followed by a 5-trial series with a conditioned light stimulus only. Control

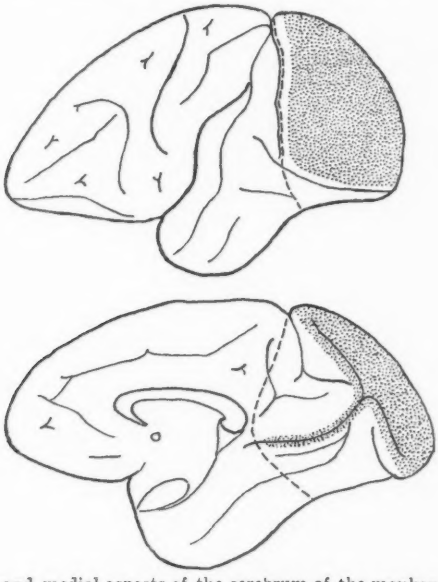

FIG. 1.—Lateral and medial aspects of the cerebrum of the monkey. The extent of the area striata according to Brodmann (1909) is shown by the stippling. The broken line indicates the line of the transection made in the removal of the occipital lobe.

records in which the monkey's eyes were shielded from the stimulating light showed no evidence at any time that the conditioned response was being elicited by secondary non-visual cues.

RESULTS.

In all the animals the extirpation of the occipital lobes was found to have removed the area striata completely. In fig. 1 the extent of the extirpation is shown diagrammatically, and in fig. 2 the post-mortem photographs of the hemispheres of one of the animals are presented.

In no instance was any cortex of the striate type found in sections through the margin of the lesion. Further confirmation of the completeness of the removal was obtained in the two animals from whose brains serial sections through the lateral geniculate body were prepared. All the cells of this nucleus were degenerated, as has been described by Poliak (1932).

Following extirpation of one occipital lobe, the monkey showed a homonymous hemianopia. The threat reflex (blinking) was absent to stimuli in the contralateral half-fields, and in running about a room the monkey bumped against objects only on its blind side. The line of division between the seeing and blind fields appeared to pass through

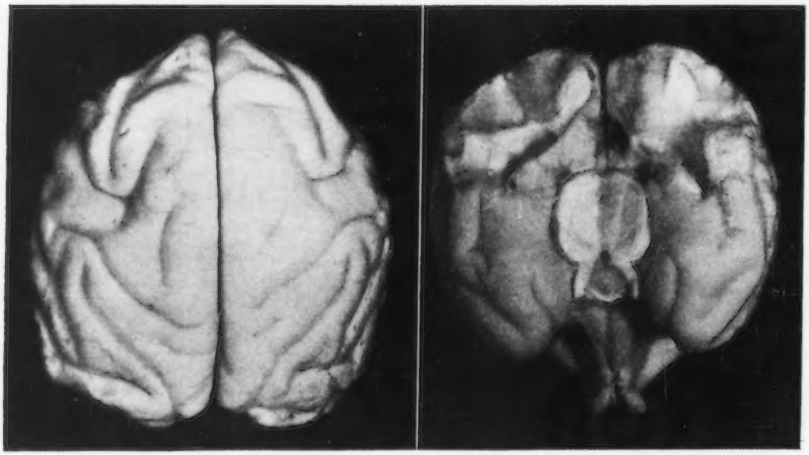

FIG. 2.—Photographs of the hemispheres of OP 5. The ventral-posterior view shows the opened lateral ventricle which was in free communication with the occipital cavity.

the fixation point. When the monkey was suitably restrained and induced to fixate its gaze upon a piece of food held directly in front of its eyes, it would not reach for a second piece of food moved from the blind to the seeing fields until the food crossed a vertical line through the fixation point. Such tests, however, could not be sufficiently accurate to permit a decision as to the presence or absence of macular sparing.

After bilateral extirpation of the occipital lobes, the monkey seemed completely blind, and our observations did not differ in any respect from those of Brown and Schäfer (1888). The threat reflex was permanently abolished, and no evidence of object vision was ever seen in any of the

PLATE I.

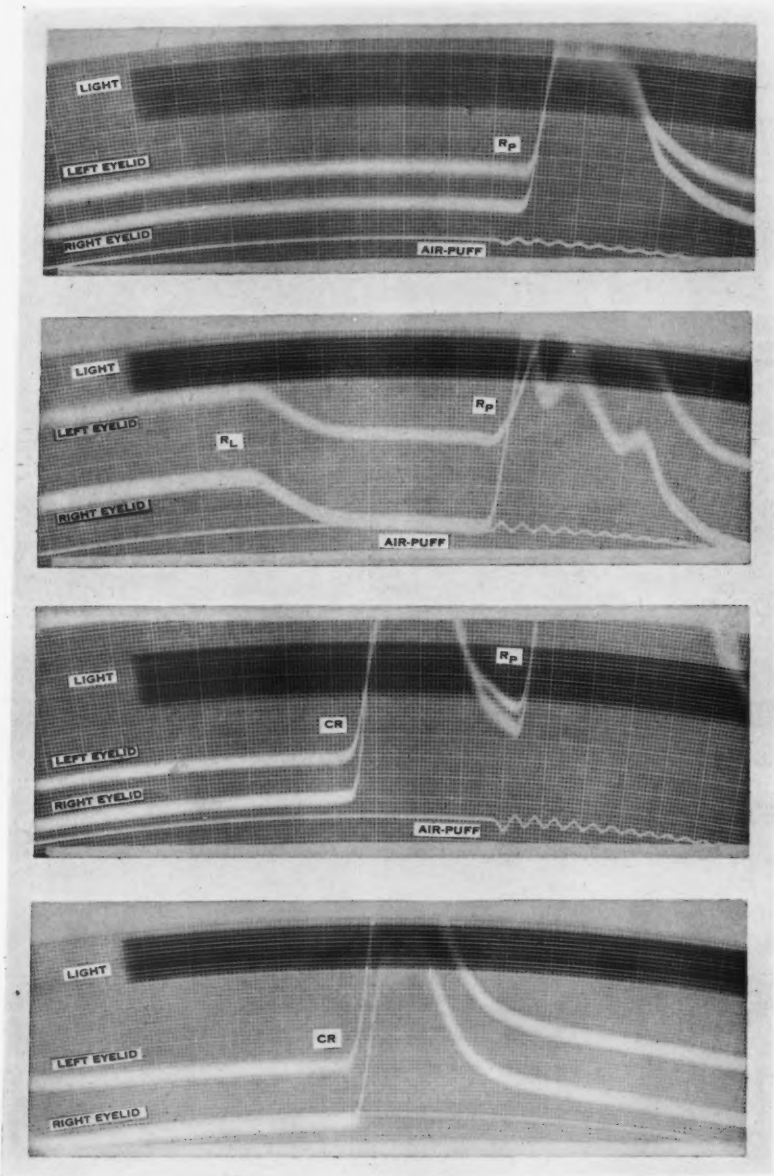

FIG. 3.—Specimen records of the process of conditioning (OP 5). The exposure of the light stimulus is recorded as a darkening at the top of the record. The unconditioned stimulus (air-puff) is recorded as a break in the lower line. Upward movement of the eyelid shadow corresponds to lid closure. Vertical time lines, 5 ms., emphasized lines, 50 ms. Record 1 illustrates the reflex (R_P) to the air-puff before conditioning. Record 2 shows the lid-opening reflex (R_L) which was present in about 20 per cent. of the trials before conditioning. Records 3 and 4 illustrate the conditioned response (CR) with and without reinforcement by the air-puff.

To illustrate paper by Donald G. Marquis and Ernest R. Hilgard.

animals. Some weeks after operation it was noted that the monkey would sometimes turn its head toward, or reach for, an object moved in the periphery of its visual field. A shadow seemed much more effective as a stimulus for this reaction than a bright light. The response, however, was so inconstant, and the difficulties of eliminating all sounds connected with the movement so great, that we were not willing to place any reliance on the observation.

The pupillary light reflex was not significantly affected. Following each operation, the pupils were equal and of normal size. The constriction to light was always present, but was restricted in magnitude for a period of one to three days following operation. Eye movements were normal with the exception of one animal (OP 11), who showed a paralysis of left lateral gaze for six days, following extirpation of the

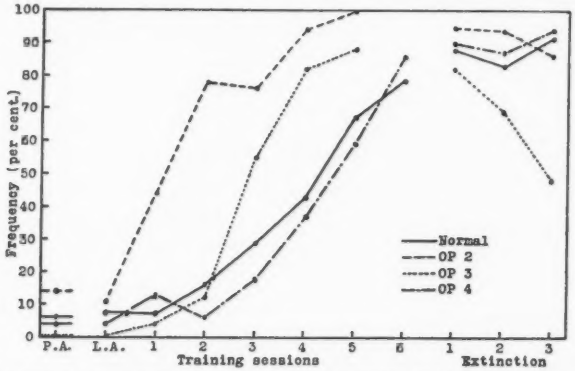

FIG. 4.—Course of acquisition of the conditioned response by three monkeys after removal of the occipital lobes, compared with the average of four unoperated monkeys. The frequency of response is plotted for the puff adaptation day (P.A.) as a control indicating the number of spontaneous responses resembling conditioned responses when no special stimulus has been presented. The light adaptation day (L.A.) yields a measure of the responses to the flash of light before conditioning. The final three days after the training sessions are retention tests without the air-puff. The expected extinction of the conditioned response when the reinforcement was omitted did not occur.

right occipital lobe. No reliable convergence or head and eye turning responses could be elicited by light stimuli.

The only reflex eyelid response to the light stimulus used in the conditioning experiments was an occasional lid opening (fig. 3, record 2), although a much more intense light sometimes produced lid closure. The reflex opening was present at a latency of 100 to 170 ms. on about one-fifth of the trials in five of the six normal animals examined. After removal of the occipital lobes only one animal (OP 3, spider monkey) ever showed the reflex opening.

Acquisition of conditioned responses after operation.—The results of the conditioning experiments stand in clear contrast to the seemingly complete object blindness of the monkey after removal of both occipital lobes. Conditioned responses to light were established in three monkeys after bilateral operation. Their characteristics may be directly compared with conditioned responses of four unoperated normal monkeys, described in a previous paper (Hilgard and Marquis, 1936). With the exception of a slight increase in the latency of the response no difference could be

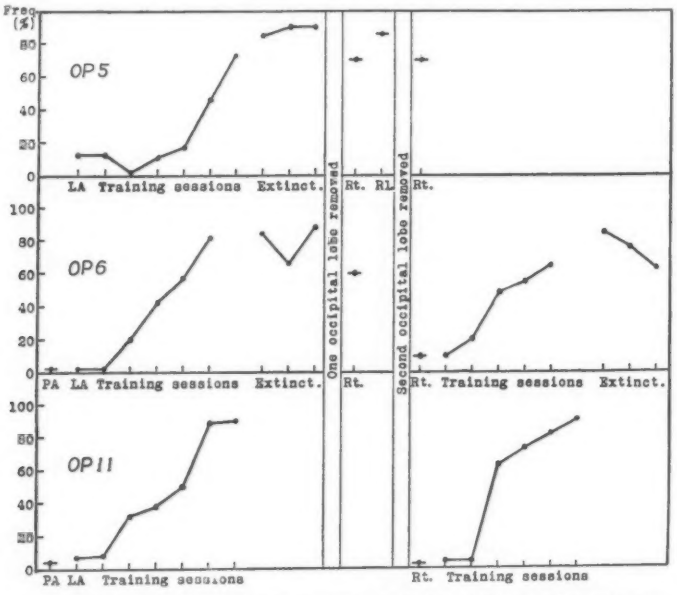

FIG. 5.—Course of acquisition and post-operative retention of the conditioned response in three monkeys. Rt. = retention test; Rl. = relearning session.

detected. The conditioned response was qualitatively identical with the normal, appearing as a brisk, complete, bilaterally equal lid closing (fig. 3). Its course of development, measured in terms of frequency of appearance during each training session, showed no deviations from the normal greater than are encountered from one normal animal to another (fig. 4). The only reliable difference found between the two sets of observations was the increased latency of the conditioned response. The mean latency for the normal animals was 196 ms., for the three animals trained post-operatively, 230 ms. (Table I).

Retention of conditioned responses after operation.—The great

similarity of the conditioned responses in the normal and in the operated monkeys is strong presumptive evidence that the neural mechanism of the response is the same in both cases, and that after removal of the occipital lobes the conditioned response is not mediated by a different mechanism functioning vicariously for the visual cortex. More conclusive evidence for this point would be furnished by the demonstration that conditioned responses established prior to operation were retained without further training after bilateral removal of the occipital lobes. This experiment has been attempted in three monkeys with somewhat inconsistent results. Since the procedures varied slightly for the different animals they will be described separately. The course of the pre-operative and post-operative training is presented in fig. 5.

In the first experiment (OP 5) there was perfect retention of the conditioned response. Before operation the response was brought to a stable frequency of 90 per cent. in nine experimental sessions. On the day following the extirpation of the left occipital lobe, the conditioned response was present and normal (no reinforcements with the air-puff are given in retention tests). Before the second operation there was a retraining session of fifty reinforcements, and retention tests on the day following removal of the right occipital lobe showed the conditioned response to be present at the slightly reduced frequency of 70 per cent.

The second experiment (OP 6) was carried out without any training between the two stages of the operation. On retention tests following the removal of the left occipital lobe, the conditioned response was present on 60 per cent. of the trials. Following the second operation, however, no conditioned response could be elicited. Retraining was instituted and the record of the development of the conditioned response presented in fig. 5 is practically indistinguishable from the pre-operative development, indicating what must have been a complete obliteration of the effects of the original training. This cannot be explained as ordinary forgetting with lapse of time, for in seven animals in which retention was tested over a rest period of three weeks, the frequency of the conditioned response decreased less than 20 per cent.

In the third experiment (OP 11) no training and no retention tests were given between operations. Following the removal of the second occipital lobe the conditioned response was absent, and redeveloped rather suddenly only after several sessions of retraining.

The present experiments do not, therefore, permit any clear interpretation of the data on retention of conditioned responses after removal of the occipital lobes. It is suggested by the observations on OP 5 that

the inter-operative training session was effective in preventing the loss of the response, although it is not clear how this is accomplished. The training consisted of only fifty trials, many fewer than were necessary for learning or for relearning in other animals. The conditioned response was present at the beginning of the session, as it was in the case of OP 6, which was also tested after unilateral operation. It might be conjectured that some modification occurred in the subcortical centres of the operated side during retraining which made retention possible after the second striate area was removed, but further experimental analysis is obviously necessary for the understanding of the loss and recovery of habits after cerebral injury.

Since retention has been demonstrated in one case to be possible, these results are interpreted as confirmation of the previous inference, based on the similarity of the normal and post-operative conditioned responses, that the visual cortex is not the essential neural mechanism for conditioning to light stimuli. The failure of retention in the other two instances must then be ascribed to some sort of shock (diaschisis) effect upon other (presumably subcortical) optic centres. Similar abolition of the effects of pre-operative training with subsequent relearning has been observed in studies of the effect of removal of the occipital lobes upon the brightness discrimination habit in rats (Lashley, 1920) and dogs (Marquis, 1934).

The greater latency of the conditioned response noted in the animals trained post-operatively was equally apparent in the retention

TABLE I.—MEAN LATENCY OF THE CONDITIONED RESPONSE BEFORE AND AFTER REMOVAL OF THE OCCIPITAL LOBES (COMPUTED FROM ALL EXPERIMENTAL SESSIONS IN WHICH THE CONDITIONED RESPONSE EXCEEDED A FREQUENCY OF 75 PER CENT.).

Monkey	Normal	Operated
OP 9	153 ms.	
OP 5	215 ,,	240 ms.
OP 6	196 ,,	238 ,,
OP 11	221 ,,	274 ,,
OP 2		216 ,,
OP 3		252 ,,
OP 4		222 ,,
Average	196 ms.	240 ms.

experiments. The latter data have a greater reliability because the observations are made on the same animal before and after operation and the differences cannot be ascribed to individual variation among animals. The mean latency of the conditioned response for each animal is presented in Table I.

During the course of development of the conditioned response the

latency decreased as the frequency of response increased. This was true of the operated animals as well as the normal animals, but the average latency never reached the normal value. From fig. 6, in which the relationship between the latency and the frequency of the conditioned response is shown graphically, it is apparent that the differential between the normal and operated animals remained nearly constant throughout the course of the conditioning.

Discussion.

The experiments reported here were undertaken to aid in the interpretation of the effects of destruction of the visual cortex in man

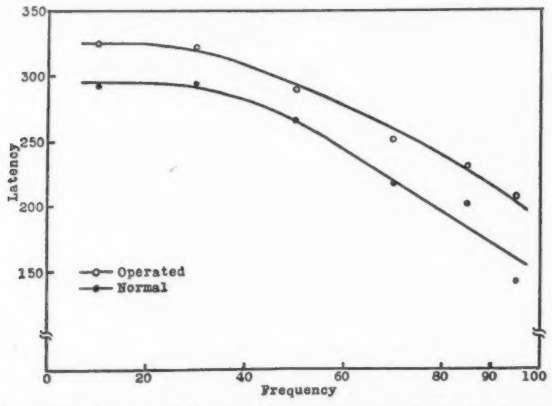

Fig. 6.—Decreasing latency of the conditioned response during its development in four normal and six operated monkeys. Each point represents the mean latency of all responses occurring on days in which the percentage frequency of response fell within the limits indicated on the abscissa.

and in other animals. The extensive utilization of animals for the experimental study of the functions of the cerebral cortex has unfortunately not been accompanied by any satisfactory basis for the application of the findings to man. When agreement between animal and clinical results is found no question is raised, but in many instances the observations cannot by their very nature be repeated on human subjects, and it is necessary to fall back on the assumption that the more similar the two species the more likely are the findings applicable to both.

There is one guide which has proved serviceable in understanding the differences in cerebral function between different animals: the

principle of encephalization, which states that in the phyletic series there is a progressive shifting of functions from lower neural levels to higher. Derived principally from comparative anatomical studies, it has been amply verified by the results of experiments on the cerebral motor area. This principle gives an indication of the direction of the difference between animals, but in its present formulation it offers no clue to the magnitude of the difference.

The principal stages in the encephalization of visual function have been outlined elsewhere (Marquis, 1934). In the lower vertebrates (fishes, amphibia) the visual correlation centre is the optic tectum of the mesencephalon. In mammals there is in addition a cortical visual centre with a projection from the lateral geniculate body. Within the mammalian series there is a progressive increase in the size, structural differentiation, and functional importance of the geniculo-cortical system at the expense of the mesencephalic centres.

Removal of the cortical visual centre in rabbits or rats abolishes the discrimination of visual form and pattern, but the animals can respond to the brightness and position of a stimulus object. Dogs are also able to discriminate light intensity after removal of the occipital lobes, but give no evidence of distinguishing position and distance. Clinical observations show that destruction of the area striata in man produces a complete blindness in which even the perception of light and dark is abolished. This significant difference between the dog and man made it desirable to investigate an intermediate species.

Directly comparable data are available for the dog and monkey with respect to visual conditioned responses. In both animals the conditioned response, after bilateral removal of the area striata is virtually unaffected. It can be established at the same rate as in normal animals, and has the same general characteristics with the exception of a slight increase in latency. In this respect, therefore, the monkey is more similar to the dog than to man, and there remains a large qualitative change in cerebral visual function between the monkey and man.

In one respect the effect of removal of the occipital lobes was more severe in the monkey than in the dog. In the latter, perfect retention of a conditioned response established prior to operation was observed in every case. Of three monkeys, only one retained the conditioned response after operation, although the other two reacquired the response with retraining.

The cerebral localization of those visual functions which remain after removal of the occipital lobes is a problem which cannot be finally

answered with the present evidence. There are several reasons, however, for believing that the conditioned responses are mediated by subcortical mechanisms rather than by extra-occipital cortical areas. Anatomical studies (Poliak, 1932) have shown that in the monkey the optic radiation terminates exclusively in the area striata, so that the only pathway of entrance to the cortex for visual impulses must necessarily have been destroyed by the removal of the occipital lobes. Furthermore, it has been shown in lower mammals (dog, rabbit) that certain visual functions persist after complete removal of the cortex, and must necessarily be subcortical. A critical test of this has not been possible in monkeys because an adequate period of survival after bilateral removal of the cerebral hemispheres has not been obtained. Visual function cannot be satisfactorily tested in the hemianopic fields following removal of one hemisphere because of the diffusion of the stimulating light to the seeing fields.

Summary.

After bilateral removal of the occipital lobes, including all of the area striata, the monkey behaves as though it were totally blind. When moving about it bumps into walls and objects, it pays no attention to food placed or moved before its eyes, and it does not blink or respond in any way to threatening gestures.

A conditioned response to a light stimulus was established in three monkeys after removal of the occipital lobes. The rate of formation of the response, as well as its form, amplitude, and frequency, were not significantly different from the normal. The only difference detected was a slight increase in latency.

In three monkeys, the conditioned response was established before removal of the occipital lobes. One monkey retained the response after operation; the other two reacquired the response with retraining.

The similarity of the conditioned responses in normal and operated monkeys provides evidence that the visual cortex is not an essential part of the neural mechanism for responses to light stimuli. This is further supported by the demonstrated possibility of retention of a conditioned response established prior to operation. While the visual cortex is necessary for all object vision depending on the spatial characteristics of the stimulation, the only discovered effect of its removal on responses to light is a slightly increased latency and an obliteration in some instances of the effect of previous training.

Comparison of the effects of destruction of the area striata in

rodents, dogs, monkeys, and man reveals a progressive encephalization of visual function in the mammalian series, with the greatest qualitative difference occurring between monkey and man. These results suggest that great caution is necessary in interpreting human cerebral function on the basis of animal experiments.

The authors desire to express their appreciation to Professor J. F. Fulton who performed the operations, and to Professor H. S. Burr for valuable aid in the anatomical studies. Part of the expenses of the research were defrayed by a grant from the Research Fund, Yale University School of Medicine.

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MUSICOGENIC EPILEPSY.

BY MACDONALD CRITCHLEY.

THE aim of this paper is to describe the occurrence of epileptiform attacks in factual association with the hearing of music.

A previous communication dealing with reflex epilepsy [1, 2] indicated that there existed cases in which auditory stimuli were capable of evoking a seizure. Whilst the majority of such cases of "acousticomotor epilepsy" were precipitated by sudden and unexpected noise, there was a small but well-defined group in which musical sounds alone were effective. Two or three illustrative cases were cited.

Opportunity has since brought to notice a series of such cases of "musicogenic epilepsy" (or "musicolepsia"), while a close scrutiny of neurological literature has added only a few additional examples.

Cases of this phenomena are too rare to permit dogmatic conclusions as to the clinical features which may be regarded as characteristic. From such evidence as is available, however, it appears that the association between stimulus and attack is a close one; only rarely does a seizure occur without the precipitating factor of music. On the other hand, music may be heard without an epileptic attack necessarily following. There is reason to believe that in some cases only certain types of music may be followed by unconsciousness. An attack does not usually follow promptly the onset of the music, and the stimulus may need to be maintained for many minutes before producing a fit. The character of the epileptic phenomena proper varies from transient "absences" or obfuscations of consciousness, to complete major attacks with convulsive movements and vesical incontinence.

PERSONAL CASES.

Case 1.—F. C., female, aged 25, consulted me in the out-patient department of the National Hospital in 1931. Since the age of 17 she had been subject to attacks of "faintness" on hearing certain types of music—particularly that produced by piano or organ. She fancied that "classical" music was more noxious than dance music, though she was not sure upon this point as she had little or no musical knowledge. She was unable to resist the attacks and was

obliged to lie down on the floor. Immediately before an attack she suffered a sense of "weakness" and pins and needles in the legs, spreading thence to the rest of the body. The feeling was a horrid one ". . . as if the nerves were all on edge." Then voices would become distant and she would remember nothing more. Once only had she micturated during an attack and bitten her tongue. On recovery she would feel very sick and usually "had a good cry." She had had as many as four attacks a day. Her previous health had been good and the family history unimportant.

Examination revealed no definite physical abnormality.

On her admission to hospital, gramophone records were played, with her consent, so that a personal observation could be made of the effects of music. At first a dance tune was tried, but she soon remarked that such music would not produce the desired effect. An orchestral record was then chosen ("Valse des Fleurs," from Tchaikowsky's Casse-Noisette Suite, played by the Berlin State Opera Orchestra). After about fifteen seconds her face took on a restless and pained expression, and the respiration became laboured. The eyelids opened and shut rapidly, and then began to flutter. She appeared distressed, her fingers clutching the bed clothes, and her lips performing rapid "smacking" movements as if she were tasting something unpleasant. Then a fixed and vacant expression became noticeable, followed at once by generalized clonic convulsions. Movements of the face were especially marked, and there was considerable frothing. The face was flushed and cyanotic; the head was deviated to the left side, the eyes being turned upwards and to the left.

At the onset of the fit the plantar responses were unobtainable; two minutes later there was a left-sided Babinski reflex, shortly afterwards both plantar responses were extensor in type. The knee-jerks were absent though the ankle-jerks were present.

Three minutes after the cessation of convulsive movements the patient opened her eyes, but seemed still oblivious of her surroundings and did not reply to questions. She rolled her head slowly from side to side.

Half an hour afterwards she was able to discuss her attack . . . "as soon as the second record started, my inside seemed to turn right over. My arms and legs went cold and numb from below upwards. I screwed up my eyes and mouth because I didn't like it. I tried to fight against it. I had no nasty taste, smell or any other uncomfortable feeling (in reply to direct questioning.) The numb feelings got stronger—then I went as if I were dead—I could no longer hear anything—and then I lost consciousness. When I came round I was alone. I've now got a vile headache."

She was kept under observation as an out-patient. Despite treatment with bromides and luminal, she contiuued to be afflicted with similar attacks, almost every one of which was precipitated by music.

Case 2.—L. P., female, aged 46, attended the out-patient department of the National Hospital, Queen Square, on account of occasional epileptic attacks of four years standing. Her previous health had been good. No abnormal physical signs could be found on examination. When questioned as to the

circumstances preceding her attacks she revealed that they would occur when listening to music, or if she became deeply interested in a conversation. The music had to be "reminiscent" in type. Old-time songs, especially if sad, were particularly provocative; dance-times did not affect her however. If she heard sentimental music being played she would not dare listen, but had to hurry out of earshot.

Case 3.—A. B., female, aged 51, consulted me on September 12, 1934, complaining of attacks of unconsciousness and also of "day-dreaming" of seven years' standing. She stated that she was quite well until one evening while listening to the music of a Radio dance-band she suddenly fell back unconscious. A month later another similar attack occurred, again while listening to the wireless. On another occasion while attending an organ recital she suddenly lost consciousness and on recovery, felt an intense headache. Thereafter she avoided as far as was possible listening to any solo music. She also became liable to attacks of "day-dreaming" which would come on in a cinema or any other place where music was being played, especially if the tune possessed a well-defined rhythm. On one occasion, a "day-dream" occurred during a patter-dance, and once also at a lecture where the speaker had an unusually monotonous and sing-song diction. She cannot describe her day-dreams, but speaks of them as nightmares in which she feels "horribly frightened," and also as if "she had been through it all before." They are momentary and, as far as she can tell, are unattended by unconsciousness. Two months ago, she had an attack of unconsciousness with convulsion and incontinence, not however preceded by music.

The family and previous histories were uneventful.

She was admitted to the National Hospital, Queen Square, where no physical abnormality could be detected. Lumbar puncture revealed a normal fluid under a pressure of 110 mm. of water.

During her stay in hospital two tests with gramophone music were carried out, on each occasion with the production of abnormal phenomena. Thus on September 27, 1934, during the playing of a rather loud fox-trot with a well-defined tempo she suddenly became pale and slightly cyanosed. She leant forward in her chair with a frightened look in her eyes (which watered a little) and she began smacking her lips. Her pulse-rate had risen to 120 beats per minute. The plantar responses were flexor but two minutes later they were both distinctly extensor in character. At this point the examiner pricked her with a pin. After about forty-five seconds she blinked her eyes and looked about her.

Questioned as to what had happened she replied "that was one of my day-dreams—like a nightmare—it was as if I had been through it all before. I was frightened of something but I cannot say what that something was." She denied any subjective alteration in vision or sensation, but she did not remember being pricked with a pin, or having her plantar reflexes tested.

The patient still continues to attend the out-patient department and still suffers from both kinds of attack (unconscious spells and day-dreams) on hearing music.

Case 4.—G. W., female, aged 33, attended the neurological out-patient department at King's College Hospital on September 21, 1934, suffering from epilepsy for the past three years.

The first attack occurred while alone in the house, listening to the wireless. She suddenly "felt funny" she could not "get her voice," everything "went black and further and further away." She felt very frightened, ran upstairs and fell unconscious at the top. She frothed at the lips but there was no biting of the tongue or involuntary micturition. A week later a similar attack occurred, again while listening to the wireless. She was then put on treatment with luminal, but one or two similar turns appeared at rare intervals, each one being precipitated by hearing music. All except one or two of her turns have occurred at the time of her periods and she has never had an attack independently of music. In one attack she bit her tongue. Her husband says that a turn starts by the patient being very frightened and she screams with terror; her face then screws up to one side and becomes distorted; one leg draws up and she then stiffens and would fall if he did not catch her. The face becomes bluish and there is a little froth at the lips. The duration is described as a matter of seconds. Afterwards she is rather dazed for half an hour.

There was nothing noteworthy in the family history or in her previous health.

Physical examination revealed no abnormality. She was however markedly nervous and apprehensive, and worried about her malady.

She was admitted to the National Hospital, Queen Square, in October, 1934, where an attempt was made to precipitate an attack by means of music.

After various records had been played for about fifteen to twenty minutes a waltz record of Strauss's "A thousand and one nights" was followed by signs of distinct uneasiness. The record was replayed and she became rather more disturbed. She put her hands over her ears, screwed up her eyes, frowned, and made numerous other nervous grimacings. She registered obvious relief when the record came to an end. When questioned she said she did not like the music, that it "sort of jarred" terribly and that if she had been at home she would have taken off the record. The sensation was not like that of the fear which usually heralded her attacks.

The patient still attends my out-patient department and at times sustains attacks after listening to music. This especially occurs at the time of her periods. Any kind of music may precipitate an attack, but especially "classical pieces, waltzes, and nice songs." She is very fond of music and possesses more than average musical taste and education.

In addition to the foregoing four cases, I have been permitted to quote the following cases by the kindness of Professor Sir Arthur J. Hall, the late Professor L. Bouman, Dr. C. P. Symonds and Dr. Fergus R. Ferguson.

Case 5.—Male, aged 22, had suffered from occasional attacks of epilepsy for some years. He was an accomplished pianist, and to his regret he found that the attacks occurred always while playing the piano. It is not certain whether attacks also occurred at other times.

Case 6.—A., male, aged 26, began to suffer from epileptic attacks four years previously. Every fit except one was associated with his playing the piano. In one attack he bit his tongue, but involuntary micturition had never occurred. He was kept under observation by Professor Bouman for the next seventeen years. Later, fits also occurred independently of music, but he continued to have attacks, as, for example, when his brother played the 'cello. Despite transitory psychoneurotic episodes, he was able to carry out his duties as the manager of an important factory with complete satisfaction.

Case 7.—V., male, had his first epileptic fit at the age of 32, after hearing a barrel-organ in the street. His second attack occurred while playing the piano. Two months later, his third attack occurred: after dinner at his parents' house, the family assembled to hear his brother play the piano. The patient quickly became uncomfortable, noticed a tinnitus, and as he was sinking into unconsciousness, was just able to call out "stop, please," before losing his senses altogether. A typical epileptic attack supervened. Other similar turns followed: once when at the opera "Lohengrin," and once again when a barrel-organ played outside his house.

The patient remained under treatment with regular small doses of bromide, and ultimately died at the age of 62, from an embolus after prostatectomy. His widow writes that her late husband suffered only three or four attacks during his married life. He largely lost his susceptibility towards music, and during his last ten years of life was able to attend concerts regularly.

Case 8.—Male, aged about 25; a wireless operator on a liner. Generalized epileptiform attacks of a minor character would occur whenever he heard a brass wind instrument play bass notes. On this account he had to transfer to smaller ships which carried no orchestra.

Case 9.—A woman who had previously been subject to migraine, sustained her first epileptic fit at the age of 25. There was a family history of migraine, epilepsy, and also of manic-depressive psychosis. Over the course of six years the patient sustained eight or nine attacks. She was a talented musician and owned a music-room. All but one of her attacks had taken place in the music-room either when she or someone else was playing the piano. The only exceptional case had occurred at a time when she was thinking out a tune "in her head." Some time later, whilst pregnant, the patient made a suicidal attempt.

Case 10.—Male, aged 40. During the War he was wounded in the right temporal region. At the age of 32 the first epileptic attack occurred. Since then, he has had about ten attacks. Two of his fits had occurred whilst listening to a concert. Another attack took place after he had been sawing for a period. The patient himself stated that when he is listening to the radio, and a certain note is sounded, he feels extremely uncertain of himself

and as though he might be going to have an attack. It is noteworthy that each of his fits is preceded by an auditory aura of a rushing or swishing noise in the left ear.

Case 11.—Dr. C. J. C. Earl has also described to me an epileptic patient of his whose attacks were always ushered in by a complicated psychological aura. Each fit was precipitated by listening to pianoforte music.

Neurological literature contains only a few accounts of epileptic attacks being produced by musical sounds. A number of these records have been published only in obscure Russian periodicals and have largely escaped notice.

Probably the first communication is that of I. P. Merzheevsky in 1884 [3]. The patient had sustained three fits provoked by melodies and musical tones new to the patient. At a concert an unfamiliar tune would produce a constriction in the throat followed by pallor. If the patient were prevented from immediately leaving the hall an epileptic fit would supervene, with biting of the tongue. When the patient grew accustomed to a melody the fit did not occur. Sometimes, a new tune provoked only dizziness, something like an aura.

A few years later, Steinbrugge [4] observed a 45 years-old patient who had had epileptic fits from the age of 15, having convulsions every time he heard music, while all other sounds, however loud, were without such effect.

The next communication was that of Y. Y. Trutovsky [5]. His patient, a man of 31, in whom an attack of epilepsy, provoked by pianoforte music, was observed during his stay in hospital. Another of his patients suffered a type of " affect-epilepsy " together with episodic periods of confusion with hallucinosis. One variety of attack was usually precipitated by violent noise of some kind ; in the hospital one such attack was witnessed being brought on by piano music.

In 1905, H. Oppenheim [6] mentioned briefly the case of a woman of 45, who was liable to two types of epileptiform attack : in the milder variety she would suddenly become anxious, and then utter a cry. The mouth then became pulled up to the right, and the right half of the body jerked ; consciousness was not completely lost. In her severer attacks there was total unconsciousness and the tongue would be bitten. Such attacks corresponded closely with the time of menstruation and occurred mainly at night, or during an afternoon sleep. When they happened during the waking state, they were always associated with music.

The most important contribution however is to be found in an

obscure paper by v. Bechterew [7], on "reflex epilepsy provoked by sound stimuli," published in 1914. Owing to the inaccessibility of the original paper, which is written in Russian, this work may be quoted in some detail. Bechterew mentions two cases, giving particulars of one. This patient was a well-known man of letters, Nikonov, who has fortunately put on record a detailed account of his own case in a manuscript, entitled, "Fear of Music." Bechterew, in his article, has reproduced this work verbatim, and excerpts may be given here: "Despite the fact that the unpleasant sensations (i.e. twitchings of the eye, palpitation, apprehension) began to recur more and more frequently—and invariably took place when I was at a musical performance alone, I bravely went to performances—I used to get disturbed by these incomprehensible twitchings of my eye and shocks in my throat to the point of perspiring all over and even trembling. However, the following incident inspired me with a real fear of music. I was present alone at a performance of "The Prophet," at the Imperial Opera Theatre in St. Petersburg. The first two acts passed without trouble. The ballet began, representing skating on ice—I felt rapid twitchings in my left eye. Then I experienced convulsions in my throat. I grew alarmed, stopped my ears, and with an effort closed my left eye, but the convulsion in my throat increased. And suddenly I felt I was losing consciousness. The twitching in my eye and the shocks in my throat, increasing, passed into a sensation of violent pain in the crown of my head, as if someone was hitting me there as hard as he could with a heavy object. Darkness enveloped me, and with the thought that the end had come, I lost consciousness. From that moment I began to experience a real fear of music—I was afraid of loud music near at hand. Then I found I had reason to fear distant and subdued music as well—eventually I found that at times even ordinary pianoforte music had the same effect on me even when played in a neighbouring flat, and I heard it through the wall. And once I experienced twitchings in my eye and shocks in my throat from the sounds of an accordion. The fear I experience when I hear music is sometimes accompanied by perspiration and palpitation of the heart. If in the street I happen to meet a military band, I display extreme cowardice, I run from it wherever I can into a side street, the gates of a neighbouring house, or to the first shop I see."

The writer proceeds to discuss what particular types of musical sound affect him most, and also to analyse the relationship of his emotional appreciation of music with the untoward subjective symptoms engendered.

Bechterew adds a note that fits recurred in this patient, each one being precipitated by music, but were ultimately cured by a course of bromide treatment.

In 1929 E. Redlich [8], writing on the psychogenesis of epilepsy, mentioned a patient in whom music, especially that of the violin, would produce a sensation of throttling going on to unconsciousness.

K. Goldstein, in 1931 [9], demonstrated a man, aged 32, who for five years had been liable to attacks lasting five to ten minutes, at first without disturbance, but later with loss of consciousness. He sometimes suffered as many as ten to twelve a day. In each attack a curious tonic state developed, with a fixed attitude and pupillary dilatation. The plantar response would be unobtainable. Each attack would be precipitated by music, and Goldstein was able to produce a tonic attack by playing a gramophone record. In the discussion which followed this communication, Bonhoeffer referred to a similar case in which epilepsy had started at the age of 30 during lactation. At first there was no precipitating factor demonstrable, but later, the fits became intimately associated with the hearing of music. The attacks were certainly epileptic in nature, and it was of interest that the patient's son was also an epileptic.

A recent paper by M. P. Nikitin [10] deals with a male, aged 30, who for seven years had been subject to nocturnal epileptic attacks. For five and a half years he became liable, during the day following a fit, to feelings like electricity passing from the right side of the chest to the head, and associated with transitory disturbance of consciousness. For three and a half years these latter sensations would take place whenever he sang a certain song, or heard someone play or sing this air, or even when he imagined the tune to himself. This had taken place on some thirty occasions. Whilst in hospital he was asked to sing this song (the aria of Zaren Berendej from Rimsky-Korsakow's "Snegurotschka"); he became cyanosed with the first few bars and then passed into a complete epileptic fit. On another occasion he was asked to sing this melody in order that a cinema film might be made, but he developed only a dreamy state, without convulsion. When singing this piece before the Leningrad Neuropathological Society, the patient sustained merely the aura in the right side.

Clinical Features.

There are therefore about twenty instances of musicogenic epilepsy available for study, including the eleven personal cases. One or two

points of clinical interest are noticeable. In the first place the age at which the epileptic phenomena make their first appearance has often been later than usual in the idiopathic varieties of epilepsy. Of 16 cases where the age of onset is known, 11 began at or after the age of 25 years. Males and females have been affected the proportion of 10 to 7; in three reports the sex was not given.

The patient's musical knowledge and appreciation may possibly be significant. My first patient could not readily distinguish dance from "classical" music, while my second was also uneducated in musical affairs. The third confessed that she was "fond of light music," though possessing very little knowledge of the subject, while the fourth was above the average in her appreciation of music. Case 5 was very fond of music and an accomplished pianist. My sixth patient described himself as very fond of music and very sensitive to the environment of the stage; he had been known to burst into tears during a performance of "Cyrano de Bergerac," and also while Sarah Bernhardt was acting. No. 7 is reported as "from childhood being always very sensitive to disharmony." The ninth was a talented executant who owned her own music-room. Goldstein's patient also appreciated music, while Bechterew's patient, "Nikonov," possessed an advanced æsthetic development and was a well-known professional critic of music.

Information as to the specific characters of the epileptogenous stimuli has not always been available. In the first case "classical" music was inculpated, whereas the second patient recognized "old-time" or "reminiscent" melodies as the most potent. My third patient stated that a well-punctuated rhythm was for her the most dangerous feature in music, and that on occasions a tap-dance or even a monotonous voice had proved effective. The fourth patient found that sentimental songs heard upon the radio were most apt to produce an attack. In this case and in the fifth, attacks might occur while the victim was playing the pianoforte. Deep notes from a brass wind instrument proved the only stimulus in the eighth case, and in the tenth case also, it seemed as though a particular note in the music proved operative. Merzheevsky specified that new and unfamiliar tunes were the only ones capable of evoking an attack. Redlich's patient was particularly susceptible to the violin. In the case reported by Nikitin, only one melody could provoke a fit, whether the patient sang this tune, or heard it played, or merely imagined it to himself. The patient Nikonov—described by Bechterew—was able to furnish the most detailed information. Here, continuous or comparatively protracted musical periods were disturbing;

most noxious of all was the so-called "musical background" as adopted by Wagner, which afforded an unrelieved and inescapable sound-procession. Loud music proved more and more dangerous than quiet; wind instruments more than string—violins, however, made an exception, and Nikonov describes their persistent high-pitched tones as "excessively intolerable." Instrumental music was worse than vocal; while slow music was more endurable than quiet lively melodies and especially those with a distinct rhythm. Dance and march music was particularly unbearable and alarming.

The character of the epileptoid phenomena has varied in these cases, ranging from a mere aura to complete major attacks with convulsions, incontinence, and biting of the tongue. Between these extremes lie the minor "absences" accompanied by transient clouding of consciousness and smacking of the lips. In Cases 1 and 3, the plantar responses were observed to change during and after an attack, from flexor to extensor, passing through a stage of being unobtainable. Goldstein's patient showed attacks which were purely tonic in character. Nikitin's patient showed on different occasions epileptic phenomena of various degree of complexity as the result of the musical stimulus.

The emotional state between the hearing of the music and the beginning of the epileptic fit is a most important factor, especially in discussing pathogenesis. Our available information is rather scanty and it is at times difficult to disentangle the affect produced by the music from the psychical aura belonging to the attack. Unpleasant, disagreeable or frightened sensations immediately before the fit are described by the first, third and fourth patients. The first of these ascribes the fear, however, to the knowledge of the impending attack. My second patient referred to a feeling of sadness just before losing consciousness, but here the mood may possibly be related to the sentimental and old-fashioned type of musical stimulus, and to its attendant associations. Patient No. 7 described his aura as a feeling of being submerged in water; a sense of insecurity "as if the surroundings had vanished." Nikonov, in his autobiographical record, said that as a boy he would feel when he heard music something like a sudden blow, a very strange and frightening sensation. Certain physical symptoms would also appear, as already described, but these were transitory and not in themselves unpleasant, though alarming because of their novelty Ever after the time when these sensations had culminated in unconsciousness, he began to develop a real fear of music. At the first hint of these premonitory symptoms he would hurriedly escape out of earshot.

In one case (No. 3) the preliminary sensations included elements other than those of fear. Something approximating to the *déjà vu* phenomenon may be read into the description. . . . "I have the feeling that I have been through it all before; as if I were going through a scene. It is the same scene on each occasion. People are there, dancing; I believe I am on a boat. The scene is not connected with any real place or event which I can recall."

An attack does not inevitably follow the onset of premonitory symptoms and some of the patients with musicogenic epilepsy develop the power of inhibiting an attack. Thus my third patient stated that if she were to hear the music without *listening* to it, no attack would follow. Nikonòv too, found that in the early days no aura would develop if he could divert his attention from the music from time to time. He was therefore more likely to experience epileptic phenomena if he went to the Opera alone. After the appearance of his first fit, he still believed that an attack was less likely to materialize if a strong emotional reaction accompanied the hearing of the music.

Pathogenesis.

Discussion of the means whereby a musical stimulus can provoke an epileptic attack is purely speculative in character. In the more common types of acusticomotor epilepsy, one usually imagines a response to the emotion of surprise or startle as the probable mechanism; obviously no such speculation can be applicable to the musicogenic cases. We seem rather to be dealing with an unusual and specific intolerance towards musical sounds, somewhat reminiscent in fact of the common dislike of music evinced by dogs. The analogy is strengthened by the occasional occurrence of convulsions in dogs as a climax of musically induced discomfort. Dr. Grainger Stewart has told me of a spaniel of his acquaintance which will fall convulsed when music is played nearby. Another such case has been described by Erlitzky [11], the dog later becoming mad; Billroth also narrates how he saw a young great dane fall unconscious when a village brass band struck up a Schutzenmarsch.

There is yet a third type of acusticomotor epilepsy which—very much rarer than the two other varieties—seems to occupy a kind of intermediate position. In this type, epilepsy is provoked by auditory stimuli of a monotonous character, and the factors of surprise as well as of musical quality do not enter. A case in point was that of E. M., a boy, aged 11 years, subject for eighteen months to minor epileptic

attacks. Although many of the fits would occur spontaneously, the patient declared that an attack would always develop if he heard a noise of a continued and monotonous order, such as an aeroplane in flight, machinery in a workshop, a kettle on the boil or wireless talks. In this case music was without effect, as were abrupt unexpected sounds; in the boy's own words, the noise "has to keep on" before a fit developed.

Some neurologists have favoured a purely mechanical view of musicogenic epilepsy and have visualized a greatly increased vascularity of the cortex produced by music, as the precipitating factor. Such a view runs counter of course to a fairly widely diffused impression that a process of local ischæmia precedes the epileptic fit. As a matter of fact, Gibbs, Lennox and Gibbs [12] were unable to demonstrate any significant change in the cerebral circulation immediately preceding the onset of seizures.

Whether music actually does increase the cortical blood-supply is not established. The physiological effects of music have not been the subject of much serious study within recent years. What data is available (Dieserens [13]; Schoen [14]), appears to show that music can produce: (1) An increased bodily metabolism; (2) either an increase or a decrease in muscular energy; (3) an irregular and accelerated respiration-rate; (4) heightened acuity of other special senses; (5) an exaltation of the knee-jerk, directly proportional to the strength of the auditory stimulus; (6) a lowered threshold for various sensory stimuli; (7) a marked but variable effect upon blood-pressure and the peripheral and cerebral circulations.

The last-named is obviously the most significant effect in relation to musicogenic epilepsy. An old human experiment described by Patrizi is of interest here. A boy, aged 13, received a severe cranial wound from an axe. The boney gap 5 in. in length allowed the pulsations of the brain to be plainly visible. Plethysmographic records were made of the cerebral pulsations and it was clearly demonstrable that an increased cerebral circulation took place under the influence of music, the effects varying somewhat according to the intensity, characters and tempo of the melody, as well as according to the pitch of a single note.

Findings such as these obviously need verification before they can be accepted unreservedly. In any event, an increased cerebral vascularity after music, even if established beyond all doubt, leaves unexplained why we do not all become convulsed on hearing music. In the same way, even if a cerebral engorgement regularly preceded a fit, two questions

would still require an answer: (1) What is it produces the paroxysmal increase in cerebral circulation?; and (2) why does not passive cerebral engorgement induced by mechanical means necessarily produce epilepsy?

It has been tentatively queried whether the hearing of music might not produce in some persons sufficient pulmonary hyperventilation to evoke an epileptic response. Some latent epileptic tendency would of course be necessary in such cases. It has been shown by Feleky [15] that various emotional states (such as might be induced by music), and particularly those of wonder and fear, can produce a marked alteration in the depth of breathing and in the inspiration/expiration ratio.

Hypotheses of this character do not bear the imprint of probability and seem far too mechanistic to account adequately for all the clinical phenomena.

From the psychological angle several suggestive points arise for discussion.

In the first place it becomes necessary to examine the suggestion that musicogenic epilepsy is merely a manifestation of hysteria. To many the occurrence of reflex epilepsy of any type raises doubt, and the mere fact that an epileptiform seizure is produced "to order" by the operation of some precipitating factor, may evoke suspicion. It is a clinical commonplace how readily the hysteric will yield to suggestion by immediate unconsciousness. The role of music, in precipitating hysterical episodes, is traceable throughout the centuries. In the mediæval epidemics of "dancing mania" or "tarantism," victims would fall unconscious and convulsed at the first notes of the appropriate music. To-day in French West Africa the Senegalese dancer will pass rapidly into an automatic state at the beat of the tom-tom, just as in Tunisia the religious ecstatics will fall foaming to the ground under the influence of their ceremonial music.

Medical literature holds records of comparable cases. Ingegnieros [16] has described a female hysteric of 26, who was a promising violin pupil. Despite the assiduity of her study she failed in her examination, and fell unconscious on hearing the bad news. Thereafter she developed a horror of the violin and would become convulsed whenever she heard that instrument played. This state of affairs was still present ten years later. Redlich, in the paper which has already been mentioned, referred to a second case of convulsive attacks associated with the hearing of orchestral music. This patient proved to be an hysteric, a locksmith whose early aspirations towards a musical career had been frustrated.

The cases of musicogenic epilepsy described in this paper are of a

different order. Some of them are accompanied by features which are traditionally regarded as criteria of "organic" as opposed to psychogenic epilepsy. Thus an extensor plantar response has been witnessed and demonstrated in at least two of the cases quoted. Incontinence of urine has occurred in some of the cases, though not in the majority. Such features would suffice, according to the present teaching, to characterize some at least of the attacks of musicogenic epilepsy as being outside the usual picture of hystero-epilepsy.

Whether, however, it is altogether wise, or indeed possible in view of modern conceptions, to attempt to demarcate sharply between "functional" and "organic" epilepsy is arguable. While clinically there are often obvious differences between the majority of attacks of epilepsy on the one hand, and of hysteria on the other, there certainly may occur attacks which cannot readily be assigned to one category or the other. Clinicians are also familiar with the occurrence of hysterical phenomena in a chronic epileptic, and it becomes difficult if not impossible at times to docket individual manifestations as "epileptic" or "non-epileptic." In any event the distinction of "functional" from "organic" is an artificial conception belonging to a past era.

It is tempting to regard musicogenic epilepsy as the operation of a conditioned reflex in the Pavlovian sense. By regarding music as the appropriate analyser, the epileptic manifestations constitute the specific response. A case such as that of Nikitin, where one tune only proved epileptogenous, offers a ready support. The suggestion would also be confirmed if in each patient there were traceable an appropriate musical background on the occasion of the first epileptic attack. Although the clinical information is incomplete in this particular, a single negative finding constitutes an important argument in rebuttal. Again, the occasional occurrence of a seizure without the operation of music, as well as the occasional failure of an attack to follow the usual musical stimulus, are both important arguments against the hypothesis of a conditioned response. We recall furthermore that in Merzheevsky's patient a tune ceased to be epileptogenous once it had lost its novelty.

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SHIVERING: A CLINICAL STUDY OF THE INFLUENCE OF SENSATION.[1]

BY R. JUNG (FREIBURG), J. DOUPE (WINNIPEG), AND E. ARNOLD CARMICHAEL.

Of the different mechanisms for the regulation of body temperature, shivering may be readily observed and is of some theoretical interest. In a paper by Uprus, Gaylor and Carmichael (1935) a method was described for inducing shivering in the human by the immersion of limbs in cold water. While it was shown that alteration in blood temperature played a prominent part in the production of the shivering, it was not possible to determine if the falling blood temperature acted directly on a "centre," or on a thermo-sensory mechanism capable of stimulating the shivering "centre." As Sherrington (1924) had discussed the part played by cold sensations in the production of shivering in animals, it was considered worth while to attempt to produce shivering in the human by a cold sensory stimulus and to investigate further the possible part played by sensation in the shivering following immersion of limbs in cold water. It is the purpose of this paper to describe the nature of the investigations, the results obtained, and to discuss the latter.

Method.

The subject was seated in a comfortable chair with the whole body exposed to the surrounding air. A draught-free tent was then built around the subject with blankets, through which the head alone protruded. The air within the tent was rapidly warmed by means of electric heaters to a stable temperature of 30° C. When the subject felt warm, his peripheral blood-vessels had dilated and the rectal temperature, which was taken by a thermo-junction, had become stable or was rising slightly, the blankets were quickly removed. At the same moment a blower made from the torso of a vacuum cleaner was turned on and blew ice-cooled air at 10 to 15° C. over the naked subject. When

[1] Work undertaken on behalf of the Medical Research Council at the Research Unit, National Hospital, Queen Square, London, W.C., while Dr. R. Jung held a Rockefeller Foundation Fellowship, and Dr. J. Doupe a Halley-Stewart Research Fellowship.

the shivering, which commenced shortly following this stimulus, became generalized and uncontrollable, the blower was turned off and radiant heat from an electric lamp was applied to the body until shivering ceased. This procedure was repeated several times on most subjects.

During the investigation the rectal temperature was recorded every fifteen seconds by means of a specially designed thermo-junction situated 5 cm. within the external sphincter. The alterations of temperature at this site were considered as indicating those of the circulating arterial blood for the following reasons. When a normal subject immerses the legs in water at 44 to 45° C. the rectal temperature commences to rise five to ten minutes before evidence of dilatation of the limb vessels takes place. If the legs are then transferred to tanks of water at 15° C. or below the rectal temperature falls. If with the subject well wrapped up in several layers of blankets to include the legs and feet so as to prevent any heat loss, the arms are placed in warm water, a rise in rectal temperature occurs. After transferring the arms to tanks of water at under 15° C. a similar fall of rectal temperature takes place as when the legs are immersed in cold water. It is unlikely, therefore, that the fall in rectal temperature depends upon the local effect of cooled venous blood returning from the legs when the legs are immersed in cold water. The site of the thermo-junction—5 cm. within the anal sphincter—also precludes such a possibility on anatomical grounds. Thus the alterations in rectal temperature as recorded in these investigations indicate the direction of change of arterial blood temperature. Accordingly the rectal temperature will be referred to hereafter as the blood temperature. In the course of some investigations the recording of the blood temperature has been supplemented by skin temperature readings from different areas and by photographic records of the finger volume. Direct observation was made as to the time of onset and cessation of the shivering, its character and the connected phenomena such as goose skin, alteration in skin colour, &c. The subjects were requested to describe any subjective sensations experienced during the investigations.

Thirty-two observations were made on twenty-seven subjects with lesions of the nervous system. Of these, nine suffered from the effect of a local lesion of one cerebral hemisphere. Four subjects had transverse lesions of the spinal cord, but in only one did the disease process completely destroy the function of the spinal cord below the level of its site. Cases of myasthenia, catatonia, Huntington's chorea, Friedreich's

ataxia, cerebellar tumour, tabes dorsalis and dyspituitarism were also investigated. Five normal healthy young adults served as controls to the above subjects. Only male subjects were used, except for one young female adult, who had a lesion destroying the spinal cord below the 4th and 5th dorsal segments. The investigations were carried out in spring and autumn and discontinued during July, August and September, as a sufficiently cool atmosphere was not then available. Reference will also be made to the records which were used for the previous paper. The shivering response elicited by the described method of cooling with cold air will be referred to as "sensory shivering." On the other hand, the shivering response induced by the immersion of the legs in cold water with a subsequent fall in the blood temperature will be called "blood temperature shivering."

Results.

A.—Normals.

Following exposure to the air of the room and the blowing of cold air over the body shivering commenced in from a quarter to five minutes. This shivering response could be elicited not only during a slight fall in blood temperature but also when the blood temperature was stable or even rising. In any one experiment the changes of blood temperature were insignificant, the fall seldom being more than 0·01° C. and the rise more than 0·02° C. In all instances the shivering ceased almost immediately following the stopping of the blower and the application of radiant heat to the body. Thus shivering was produced in normal subjects by a cold sensory stimulus to a wide area of skin and was found to be independent of the direction of blood temperature change: further, the application of a warm cutaneous stimulus immediately on cessation of the cold draught caused the shivering to stop forthwith.

B.—Abnormals.

A general survey of all the investigations showed that the facility of producing sensory shivering varied widely in different individuals: a short latent period and a long prolongation of shivering after cessation of the cold stimulus were seen in subjects with differently situated lesions of the nervous system, as well as in normal persons. It appeared that the facility to shiver was dependent more on the general physical condition (increased readiness to shiver in ill and poorly nourished individuals and the opposite in strong and fat persons) rather than on the presence of any focal lesion of the nervous system. Even in deeply

stuperous catatonic patients sensory shivering as well as blood temperature shivering could be elicited by adequate stimuli. Nearly half the observations were done in the morning when the subjects had a relatively low body temperature (generally below 37° C.) and the remainder in the afternoon with a relatively high body temperature (generally above 37° C.). No conspicuous differences in the time of onset of shivering could be observed in these two groups, so that it may be assumed that sensory shivering is independent of the actual blood temperature, provided it has not been artificially lowered.

C.—Afferent Mechanism.

That the stimulus for the shivering was in fact the sensory cold stimulus was demonstrated as follows. The subject with destruction of the spinal cord and consequent anæsthesia below the level of the lesion was submitted to the following procedure. During a gradual fall of 0·02° C. in blood temperature, the insentient part of the body was exposed to the cold air draught for seven minutes; no shivering resulted. The blood temperature then commenced to rise and while in this state the sentient part of the body was exposed to the cold stream of air; within a minute and a half shivering limited to the muscles innervated from above the level of the lesion, commenced and continued until the blower was turned off and radiant heat applied. While the cold air was directed on to the normal skin, the subject complained of coldness, saying "It is cold." The cold sensation was referred to the surface of the sentient skin. Immediately the radiant heat was applied, the cold sensation rapidly changed to one of warmth.

From these observations it was apparent that a cold cutaneous sensation produced shivering and that a similar stimulus to an anæsthetic region failed to give rise to shivering. Thus the shivering produced by a stream of cold air was dependent upon afferent impulses coming from the skin.

To determine if hyperæsthesia to cold in any way modified the shivering responses, two subjects were investigated, one suffering from tabes dorsalis and the other from a lesion of the thalamus. In both subjects marked hyperæsthesia to cold was demonstrable clinically. The stream of cold air caused the subject with tabes to jump immediately, as if he felt it as an almost painful stimulus. Shivering, however, did not commence for four and a half minutes and ceased one minute after the blower was turned off and the radiant heat applied. During this period the blood temperature rose 0·01° C. At a later period, with a

stable rectal temperature, shivering was produced within one and a half minutes. In the subject with a lesion of the thalamus shivering resulted one minute after the application of the cold air and ceased within two minutes of the application of the radiant heat. In neither subject was the shivering more intense than in the normal.

Thus hyperæsthesia to cold does not alter significantly the time of onset of shivering following the application of a stream of cold air to the body.

D.—Efferent Mechanism.

Spinal lesions.—It has been shown that following the sensory stimulus of cold to the sentient parts of the subject with a complete lesion of the spinal cord, shivering only occurred in the muscles innervated from above the level of the lesion. Similar observations were made on two other subjects with transverse lesions of the spinal cord following fracture of the vertebræ. On two occasions a subject, in whom the spinothalamic tracts had been severed at operation for the relief of pain, was exposed to the stream of cold air. This caused shivering, though on each occasion there was a rising blood temperature. Both times the shivering was limited to the muscles receiving a nerve supply from segments above the level of the incisions in the spinal cord. Sensory shivering is therefore limited to muscles receiving a nerve supply from above the level of a complete lesion of the spinal cord or above the level of section of the antero-lateral columns.

Pyramidal lesions.—In eight subjects with damage to either one or both pyramidal tracts sensory shivering was provoked and occurred in all the muscles of the arms, trunk and legs.

From these observations it is apparent that shivering is independent of the integrity of the pyramidal tract and is absent below the severance of the anterolateral columns. Sensory shivering has for its production the same efferent pathways within the spinal cord as blood temperature shivering; these pathways lie in the anterolateral region of the spinal cord.

A further study was made of the effect of lesions situated elsewhere than in the spinal cord on sensory shivering.

Cerebellar lesions.—In a subject suffering from Friedreich's ataxia, and in whom sensory shivering was produced during a slight rise in blood temperature, it was found that in place of the clonus-like movements seen in a normal subject the movements were irregular and were best described as choreiform. These choreiform movements were also observed in a subject with a cerebellar tumour when they were limited

to the limbs on the same side as the tumour. That the integrity of cerebellar function is necessary for the production of the clonus-like movements of shivering is the deduction made from these observations.

Defective deep sensibility.—When the subject with tabes, who exhibited deep sensory loss in the legs including the senses of position and passive movement, was investigated, the cold stream of air produced well-marked clonus-like movements in the arms; but in the legs the movements were more irregular and jerk-like, varying considerably in range, and were later in onset. Thus absence of deep sensation from a limb altered the time of onset and character of the movement of shivering. Summarized, the clonus-like movements of shivering require the functioning of the cerebellum, its connections and the afferents coming from the muscles.

Lesions of the cerebral hemisphere.—Nine subjects, each with a discrete lesion limited to a cerebral hemisphere, were examined. The lesions in each individual varied as to site, but in one or other subject all areas of the cerebral substance were included. In two subjects it was only possible to produce sensory shivering when there was a slight fall of blood temperature; in the other seven, sensory shivering occurred during a rise in blood temperature or while it remained stable. Though no preference for one side or the other to present shivering early was constantly observed, sensory shivering tended to show itself more constantly and a few seconds earlier in the muscles of the limbs which were spastic. It was similarly noticed that in subjects suffering from amyotrophic lateral sclerosis the muscles of the limbs exhibiting marked spasticity showed the clonus-like shivering movements more readily than the others. In assessing the effect of lesions of the pyramidal tract on sensory shivering, it should be remembered that variations in posture of a normal subject will affect the time of onset and the degree of shivering. Thus no conclusive evidence could be obtained from the study of this series that sensory shivering was in any way influenced by lesions of the cerebral hemispheres, apart from the fact that muscles of any spastic limb tend to show clonus-like movements easily.

E.—Relationship between Sensory Shivering and Blood Temperature.

For a detailed study of the influence of sensation on shivering and the relationship of the shivering produced by the two methods, a subject with complete anæsthesia below the 4th and 6th dorsal segments

was investigated. It has already been demonstrated that the sensation of cold caused shivering in this subject while the rectal temperature was rising slightly. On another occasion shivering was initiated by blowing cold air over the sentient parts of the body during which there was a slight fall of 0·02° C. in the blood temperature. This shivering was then stopped by the application of radiant heat to sentient parts of the body, and when the shivering ceased the anæsthetic legs were placed in a tank of water at 13° C. During the next thirty minutes the rectal temperature fell 0·7° C., but as long as the radiant heat remained applied to the upper part of the body, no shivering occurred. After a fall of blood temperature of 0·4° C. the subject complained of an internal cold sensation in the chest, which gradually increased to a feeling of "cold through and through." She said, "I am cold." The blood temperature, having fallen 0·7° C. began to rise, presumably owing to some internal heat-regulating mechanism, as the legs were still immersed in cold water. At the time of cessation of fall of blood temperature a few fibrillary twitches lasting less than half a minute were observed in the pectoral muscles. As the blood temperature rose, the cold internal sensation disappeared. From these observations it may be deduced that a fall in blood temperature and an internal cold feeling need not necessarily be followed by shivering when at the same time the sentient areas of the body are exposed to a warm stimulus.

The same subject was investigated further. With the face, upper limbs and chest uncovered, the anæsthetic legs were immersed in a tank of water at 42° C., which produced a rise in blood temperature of 0·3° C. The legs were then transferred to water at 9° C. with the result that two minutes later the blood temperature began to fall rapidly. Eight minutes later, after a fall in blood temperature of 0·63° C. shivering commenced and rapidly became generalized and uncontrollable. Several radiant heat lamps were then switched on and directed to the exposed and sentient parts of the body. During the course of the next eight minutes the shivering gradually became less and eventually ceased altogether, though the blood temperature had continued to fall a further 0·65° C. At this stage the subject ceased to feel cold on the surface of the body though she appreciated a cold internal sensation. The lights were then switched off and within thirty seconds the shivering recommenced, becoming as severe as before, and the subject complained of feeling cold all over. The legs were then transferred to water at 42° C., which caused a rise of blood temperature after an interval of four minutes. The shivering continued, but gradually became less,

ceasing altogether when the blood temperature had risen 0·7° C. from its lowest point. During the fall in blood temperature and irrespective of the warmth applied to the surface by the radiant heat lamps, the subject felt a cold internal sensation.

From these observations it is apparent that the shivering accompanying a fall in blood temperature may be completely abolished by a warm stimulus applied to the sentient parts of the body. Thus an adequate warm cutaneous sensation will inhibit shivering, though the blood temperature is falling and there is an internal feeling of cold.

An attempt was then made to induce shivering during a rise in blood temperature. For this purpose the legs were immersed in water at 42° C., which caused a rise of 0·35° C. in blood temperature in twenty minutes. While the blood temperature was rising, the stream of cold air was applied to the upper parts of the body. This resulted in shivering occurring two minutes later on one occasion and three and a half minutes later on another occasion. The second time, immediately the stream of cold air ceased and radiant heat was applied, the shivering stopped. At this point the legs were removed from the tank of warm water and the blood temperature allowed to fall slowly. The stream of cold air was then applied and within one minute shivering commenced.

That the shivering response produced by a stream of cold air may still be obtained though the blood temperature is rising is apparent from these observations. It is also to be noted that sensory shivering was more easily produced when the blood temperature was falling.

As these observations had shown that the shivering associated with a rapid fall in blood temperature could be inhibited by a continuous warm stimulus, an attempt was made to produce in a normal subject a fall in blood temperature without applying a severe cold cutaneous stimulus. On several occasions shivering was produced in one subject by the immersion of the lower limbs in cold water at 9° to 12° C. With a room temperature of 22° C. immersion of the legs in cold water at 9·1° C. was followed three minutes later by shivering, the blood temperature having fallen 0·06° C.; again, with a room temperature of 36·5° C. immersion of the legs in cold water at 12·1° C. resulted in shivering six minutes later, though a fall of only 0·03° C. had taken place in blood temperature. Thus with a warm or cold surrounding temperature shivering was easily provoked by plunging the legs into cold water. To determine if the fall in blood temperature was the provoking agent rather than the cold cutaneous stimulus resulting from the immersion of the legs in water at 9° to 12° C., the following

investigation was carried out. The same subject, after a preliminary period of warming, transferred the legs from the bath of water at 44·5° C. to one of water at 30·5° C. The subject stated that the water felt "cool" but not cold. Within eight minutes the blood temperature had fallen 0·32° C., without any shivering. At the end of this period the legs were immersed in water at 15° C., whereupon shivering immediately commenced. The sensation following immersion at this lower temperature was described as "very cold."

As in the first two experiments a fall of blood temperature of 0·06° C. or less was followed by shivering and in the last experiment a fall of 0·32° C. was not followed by shivering, the shivering could hardly result from the falling blood temperature. The factor, common to all these experiments and followed by shivering, was the immersion of the legs in cold water at 15° C. or below. Therefore the cutaneous sensation of cold was apparently the provoking stimulus in this subject.

Finally the records of previous experiments set forth in the earlier paper were reviewed. It was found that with insentient legs immersed in cold water shivering only occurred after a fall of 0·5° C. in blood temperature, while in normal subjects a fall of 0·1° C. was followed by shivering. Similar observations were made in the present series. The marked difference in the time of onset of shivering between those with normal sensation in the legs and those without indicates further that when the legs of the normal subject are immersed in cold water the resultant shivering is dependent more upon the sensation of cold from the legs than on the fall of blood temperature.

Discussion.

In addition to shivering produced by immersion of the limbs in cold water it has been possible to provoke shivering in subjects by cooling the surface of the body with cold air. The shivering so provoked occurred during a stable blood temperature or even when the blood temperature was slowly rising. Therefore a causative factor of shivering other than changes in blood temperature had to be assumed. As the shivering followed a cold stimulus to the skin it appeared that this was the factor. This assumption was shown to be correct, for a stream of cold air produced shivering when directed on to normal skin and no shivering when directed on to anæsthetic skin.

The motor characters of the shivering produced by the sensory stimulus of cold air both in the normal and pathological subjects were essentially the same as those of shivering following immersion of limbs in cold water. The presence of shivering in subjects with lesions of

the pyramidal tracts indicated that sensory shivering was independent of the integrity of these tracts. As sensory shivering was absent below the level of the incision of the antero-lateral columns in the spinal cord, it is necessary to postulate that the efferent pathway for shivering lies in this region of the spinal cord. In this respect the efferent pathway for sensory shivering is the same as for blood temperature shivering. It has been further shown that the character of sensory shivering is modified by lesions of the cerebellum and its connections, again resembling blood temperature shivering. It may therefore be presumed that the two methods of provoking shivering both require the same efferent pathway and the integrity of the cerebellar mechanism for its clonus-like character. It has further been shown that the clonus-like character is altered by a lesion of the sensory fibres from the limbs.

Lastly, it has been shown that lesions of the substance of the cerebral hemisphere do not significantly alter the shivering response to a stream of cold air—thus having a similarity to blood temperature shivering. In experiments on animals Pinkston, Bard and Rioch (1934) observed that shivering occurred more readily after bilateral ablation of the fore-brain. They also noted in a limited number of experiments that following unilateral ablation shivering "was entirely symmetrical." With the latter observation those in the present paper are in agreement. Aring (1935) reported that in monkeys and baboons there was a "significant deviation" of the shivering responses following removal of "motor area (Area 4)." In these animals shivering was more easily provoked but remained symmetrical. The symmetry of the shivering responses in man with hemiplegia is in accord with these animal experiments.

It is now necessary to determine if the underlying affector mechanism be the same or different in the two methods of producing shivering. The part played by sensation in the production of shivering has been discussed by several authors. Sherrington (1924) believed from his experiments on dogs that changes in blood temperature played a prominent part in the production of shivering. On the other hand, Liebermeister (1860), Ebbecke (1917) and others considered that the heat-regulating mechanism of the body, including shivering, were dependent for their delicate control on sensory impulses. In the investigations reported in this paper it has been shown that shivering associated with a fall in blood temperature produced by the immersion of anæsthetic legs in cold water may be inhibited completely by a warm sensory stimulus, or once provoked, can be stopped by a warm cutaneous stimulus, although the blood temperature continues to fall. Again, in subjects with absence

of sensation in the legs, shivering only follows a fall of 0·5° C. in blood temperature when the legs are immersed in cold water; at this period the subject feels cold. On the other hand, in normal subjects a fall of only 0·1° C. in blood temperature is associated with shivering when a cutaneous sensation from the cold water accompanies the fall: if, however, this intense cold sensory stimulus is avoided by immersing the legs in water at 30·5° C. a greater fall in blood temperature occurs without shivering. Further, it has been shown that shivering can be provoked during a rise in blood temperature by a cold sensory stimulus. For these reasons it appears that sensory impulses are much more productive of shivering than a fall in blood temperature. In fact, it is only in very extreme circumstances that a fall in blood temperature of a sufficient degree will alone produce shivering and when it does the subject has experienced a subjective sensation of internal cold, which suggests that sensory afferents are already in play. These observations, therefore, favour the view that the sensory impulses of cold from a wide area of the body comprise the effective stimulus for shivering when it is provoked either by immersion of the limbs in cold water or by a stream of cold air applied to the body.

SUMMARY.

A method has been described of provoking shivering without lowering the blood temperature.

Shivering so provoked has the same characters as shivering associated with a fall in blood temperature. The efferent pathways are the same.

Evidence has been produced which favours the view that shivering, associated with a rapid fall in blood temperature, results from sensory impulses rather than from changes in blood temperature directly acting on a "centre."

We desire to express our thanks to those members of the Honorary Staff of the Hospital who so kindly permitted observations to be made on patients under their care. Dr. C. D. Aring kindly assisted in several of the investigations and for his help we are grateful.

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SYMPATHETIC GANGLIONIC RESPONSES IN MAN.[1]

BY B. BOLTON, D. J. WILLIAMS, AND E. ARNOLD CARMICHAEL.

BEFORE making a study of the possible part played in man by the spinal segments in vasomotor responses, it is necessary to determine if there is a response dependent upon an afferent fibre which passes direct to the sympathetic ganglion and is there in synaptic connection with the efferent cells. It is the purpose of this paper to describe the investigations undertaken and to discuss the results obtained.

METHOD.

In two subjects plethysmographic records were taken from the digits of the hands and feet by a method previously described by Bolton, Carmichael and Stürup (1936). Vasomotor responses were elicited by various sensory stimuli while the subject was in both a cold and a warm state.

OBSERVATIONS.

Subject A., aged 16. Nine months before admission to hospital, during the course of twenty-four hours, she developed a complete paralysis of both legs. On examination the legs were found to be in a flaccid state with no tendon reflexes. The muscles of the lower abdominal wall, thighs, calves and feet were wasted. There was a complete loss of all forms of sensation up to the lower level of the 5th dorsal segment on the right side, and the 4th dorsal segment on the left side.

Local injury to the skin of the abdomen, thigh and calves, as produced by stroking with a blunt pencil, caused a well-marked flare. Faradic stimulation of the skin over these areas resulted in a pilomotor response over an area of roughly 3 cm. diameter. The flare following injury indicated that the posterior root ganglia and the peripheral portion of the sensory nerves were undamaged; further, the post-ganglionic pilomotor fibres were also intact, otherwise it would not have been possible to obtain a faradic pilomotor response. When exposed

[1] Work undertaken on behalf of the Medical Research Council at the Research Unit, National Hospital, Queen Square, London, W.C., while Dr. D. J. Williams held a Halley-Stewart Research Fellowship.

to the atmosphere of a cold room at 17° C., and following immersion of the left upper limb in a tank of cold water which caused a drop of 0·45° C. in rectal temperature in twelve minutes, the temperature of the toes remained between 33° and 34° C. Such a procedure caused a fall in temperature of the fingers of the right hand from 33° to 25° C., when the experiment was terminated. The persistent dilatation of the vessels of the toes, as indicated by a steady skin temperature of 33° C., may result from interruption of either the pre-ganglionic or post-ganglionic fibres to the vessels of the toes. It has been shown in this subject that the post-ganglionic pilomotor fibres were still present. As the cell stations for the pilomotor post-ganglionic fibres are in the sympathetic ganglia, these sympathetic ganglia must necessarily be intact. Also situated in the sympathetic ganglia are the cells of the vasomotor post-ganglionic fibres ; it may accordingly be deduced that in this subject these post-ganglionic vasomotor fibres were also intact. The persistent state of dilatation of the vessels of the toes was therefore dependent upon an interruption of the pre-ganglionic fibres or to a destruction of the cells of these fibres as they lay in the lateral horn of the spinal cord. As the lesion from clinical evidence was essentially spinal, it was more likely that the latter event was the correct one. In favour of this was the observation that the muscles of the abdomen and legs were wasted, the result of destruction of the anterior horn cells. In this subject, then, it may be safely deduced that there was an intact peripheral sympathetic ganglionic system. As the sensory peripheral fibres were also intact, this subject was ideal for the study of possible ganglionic responses.

In a warm state, plethysmographic records were obtained from the digits of one hand and both great toes. Stimulation of the skin with a nerve supply from above the level of the spinal lesion caused vaso-constriction only in the finger. When similar stimuli were applied to the anæsthetic skin, no responses were obtained either in the fingers or in the toes. Severe pressure of the leg muscles and distension of the rectum by a balloon produced no effect in toe volume; further, during long periods of an hour or more no variation of toe volume occurred, though during these periods active intestinal movements were present, as evidenced by marked borborygmi. Thus in this subject it was not possible with the stimuli used to produce a response in the legs. This interpreted indicated that no stimulus could reach the sympathetic ganglia direct by an afferent fibre and there stimulate the sympathetic vasomotor cells. In other words, there was no ganglionic response.

Subject B., aged 24. In an accident he was injured in the lumbar region, where there was X-ray evidence of a fracture dislocation of the 1st and 2nd lumbar vertebræ. As a result of this injury there was a flaccid paralysis of the legs, with wasting of the muscles of the feet, calves and left quadriceps. The ankle and knee jerks were absent. All forms of sensation were lost on the left side over the distribution of lumbar 2nd root, the remaining lumbar and sacral roots and on the right side from and including the 4th lumbar root. At operation the roots of the cauda equina were found matted together and grey, some actually being torn.

Following a local injury, as produced by drawing a blunt object fairly heavily along the surface of the insensitive areas of the skin, a definite flare developed. The presence of the flare indicated that the posterior root ganglia cells and the peripheral portion of the sensory nerves to the anæsthetic skin were also intact. When this subject was warmed by immersing the upper limb in a tank of water at 44 to 45° C., which produced an adequate rise in rectal temperature, the temperature of the two big toes exposed to a room temperature of 21° C. rose rapidly after a period of four minutes and reached a temperature of 33° C. in nine minutes. When the upper limb was transferred to a tank of water at 12° C. the temperature of the toes fell rapidly. In this way it was possible to demonstrate that the blood-vessels of the toes were under the control of the sympathetic vasomotor nerves; in other words, no damage had occurred to the vasomotor pre-ganglionic fibres emerging in the lower dorsal and first lumbar anterior roots, to the sympathetic ganglia or to the post-ganglionic fibres to the vessels of the toes. The wasting of the muscles of the legs followed upon the destruction of the anterior roots as they lay in the spinal canal. In this subject, then, the pre-ganglionic and post-ganglionic fibres were intact, but the path for afferent impulses from the legs was interrupted central to the posterior root ganglion, leaving the peripheral part of the sensory neurone intact. This second subject permitted a further investigation for ganglionic responses as the nervous control of the blood vessels of the toes was intact.

The subject was then examined for vasomotor responses in the vessels of the large toes and an index finger. In a cool state with the peripheral blood-vessels constricted and in a warm state with the vessels dilated, various sensory stimuli were applied to the normal and anæsthetic skin areas. In the cold state no alterations of the plethysmographic records were obtained, irrespective of the site or nature of the sensory stimulus. In the warm state, stimuli such as a pinch, pressure and cold applied to the normally sensitive skin produced a vasoconstrictor

response in the digits of the hand and both feet. Visceral pain from pressure of the testicle resulted in similar vasoconstriction. When the anæsthetic area was stimulated by stronger stimuli, including severe deep pressure, no responses occurred in the digits of either the upper or lower limbs; stimulation of the dorsalis pedis artery on the one side by a faradic current produced no response in the digits of the other lower limb; similarly, stimulation of the terminal branch of the anterior tibial nerve on the same side failed to produce vasoconstriction in a digit of any limb, including the limb stimulated. Thus in this subject stimulation of the lower limb failed to produce any vasomotor response either in that limb or in the upper limb.

As the examination of the subject had demonstrated no lesion outside the spinal canal, it appears that if an afferent fibre coming from the legs terminates within the sympathetic ganglia supplying the leg, it has been impossible to bring it into functional activity by the methods employed. Thus no sympathetic ganglionic responses were demonstrable in this subject. That vasoconstrictor responses could be obtained in the toes following stimulation of the sentient parts of the body indicates that the afferent impulses pass centrally to the cells in the lateral horn in the spinal cord either directly or via several neurones. There, stimulation of the lateral horn cells causes impulses to pass out to the motor cells in the sympathetic ganglia, the activity of which causes vasoconstriction. The absence of responses by stimulating the legs in this subject and the presence of the responses by stimulating normal skin clearly indicates that vasomotor responses are dependent upon an arc, which includes elements within the central nervous system.

Discussion.

In recent years renewed attention has been paid to the possibility of synaptic connections between afferents and sympathetic efferents within sympathetic ganglia. Schwartz (1934), using the psycho-galvanic reflex (skin resistance), demonstrated an alteration in the reflex when pressure was made on a limb which had been de-afferented and had had all the white rami going to its sympathetic ganglia cut. When all the grey rami were also cut, no response occurred, but the skin resistance by this procedure had risen from 8,000 to 15,000 ohms. The results which he obtained do not necessarily indicate a ganglionic reflex and are explicable upon a basis of altered circulation produced by the pressure on the limb, for Goadby and Goadby (1936) showed that the psycho-galvanic reflex (skin resistance) was dependent upon the blood supply and was not

necessarily evidence of a nervous reflex. Wernφe (1925) deduced from his experiments on fish that a sympathetic ganglion cell might have two neurones; one passing to the gut wall and the other to the integument, both being motor. Following stimulation of the gut, alteration of pigment distribution took place in the periphery. It is difficult to accept this hypothesis as it means a motor ending may also act as a sensory ending. On the other hand Bain, Irving and McSwiney (1935) have shown in a series of carefully controlled experiments on cats that there is no synaptic connection between an afferent fibre from the gut and the cells within the sympathetic ganglia.

The experiments described reveal results in line with this last viewpoint. In the first subject with intact sympathetic ganglia and peripheral sensory neurones, but a damaged spinal cord destroying the cells in the lateral horn it was impossible to produce any vasomotor responses in the legs. In the second subject, in whom it was possible to demonstrate that the sympathetic ganglia were functionally intact and in whom the afferent fibres were destroyed as they entered the cord without damage to the cord, again no vasomotor responses were obtainable by stimulating the anæsthetic zone. Thus, to produce in man a vasomotor response it is necessary for the afferent fibre to reach the spinal cord and within the central nervous system to connect either directly or by connector neurones to the cells of the lateral horn. It has not been possible to produce a vasomotor response when sensory neurones and sympathetic ganglia were intact and the cord or attachment of the sensory neurone to the cord destroyed. This indicates that no ganglionic vasomotor responses in man could be obtained.

Summary.

In man no evidence has been obtained to favour the presence of ganglionic vasomotor responses.

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THE ORIGIN AND MECHANISM OF PAROXYSMAL NEURALGIC PAIN AND THE SURGICAL TREATMENT OF CENTRAL PAIN.

BY CHARLES H. FRAZIER, F. H. LEWY AND S. N. ROWE
(From the Neurosurgical Department of the Hospital of the University of Pennsylvania).

Is it justifiable to regard neuralgic pain as a specific unit? This seemed to have been the case when Henle [4] in 1853 wrote: "Neuralgia means pain for the explanation of which a lesion of the corresponding peripheral nerve cannot be demonstrated." Histological methods have since improved and simultaneously our knowledge of the pathology of the nervous system. At present the trend is to add more and more cases, previously diagnosed as neuralgia, to the chapter of neuritis. In the new edition of the "Handbuch der Neurologie" [6] (1935) the title "neuralgia" is confined to typical and atypical trigeminal neuralgia, to occipital, and to some unusual forms of brachial and intercostal neuralgia. Even this arrangement seems to require some sort of apology, for absence of pathological changes in the methods of to-day may not mean the same in the technique of to-morrow. And should we not assume the origin of neuralgia pain to be in the peripheral nervous system, realizing that section of the nerve, distal or proximal to its ganglion, relieves the pain permanently?

Careful examination of patients with trigeminal neuralgia, with tabetic crises or with thalamic pain, however, must convince the observer that the characteristic symptoms and signs of this group are entirely different from those caused by the neurolytic swelling of so-called neuritis.

Pain plays an important part in medicine. New ways and means of surgical intervention for relief of pain not thought of a half century ago, have been discovered and described (retrogasserian neurotomy, cordotomy, rhizotomy). The basic problems of the physiology of pain, however, are not yet solved. This is understandable when it is considered that pain and its characteristics are purely subjective phenomena. The possibility of experimental investigation in animals is limited. We may try to find a point of attack through careful analysis of patients showing

disturbances of sensibility, but we are also bound to seek opportunities to observe the course of physiological experiments presented by nature itself.

In 1934, by means of graduated hairs and thorns and by chronaximetry, we examined the sensibility of fifty patients suffering from trigeminal neuralgia before and after retrogasserian neurotomy [5]. The results suggested the presence of lesions situated in the thalamocortical sensory system. Serial anatomical examination of the brainstem in three cases seemed to corroborate this hypothesis. Various considerations and clinical data fitted well into this assumption, but we hesitated to base a positive conclusion upon three cases, and the chance of obtaining additional autopsy material in an operation with a mortality of less than one half of one per cent. was small. We were fortunate, however, in having an opportunity to observe a patient whose treatment enabled us to confirm our conception of the origin of trigeminal pain from an entirely different angle. Beyond this special problem of facial neuralgia we got a first glimpse into the mechanism of central pain as a whole, and could attempt its relief.

Case Report.

Mrs. K. (File No. 31606), aged 64, a very intelligent woman, for twenty-five years following acute muscular rheumatism suffered from high blood-pressure (210/100) accompanied by myocardial degeneration, diabetes, headache, scintillating scotoma, and pains in the eyes, until in 1933 she had a "stroke." At that time she developed a complete left-sided hemiplegia with dysarthria, and immediate excruciating pain in the entire left side of her body from the vertex over her face, thorax, abdomen, and extremities down to the toes. While the hemiplegia and dysarthria improved to practically normal function, the pain persisted and defied all therapy. At the time of her admission to the Hospital of the University of Pennsylvania the patient was consuming up to 9 gr. of morphine daily without complete relief of pain.

Two forms of pain were differentiated by the patient:—

(1) A constant intense pain "as if red-hot lava were running over her shoulder, hands and toes," or "as if hot lead were being poured into the palm of her hand." At the left side of her face she felt a "sensation as if icy water was trickling over the cheek," or "as if an ice plate was being pressed against the face." At other times the fingers of the left hand and the left side of the trunk, especially in the lower quadrant, "felt as though they had been smashed with a hammer." All over the left side was an excruciating sensation "as if the skin were drawn just as tight as could be."

(2) Twice or three times a day a paroxysm occurred during which the patient experienced electric shocks passing through the left side of the body.

Despite this spontaneous pain and dysæsthesia there was an extensive though not complete anæsthesia and analgesia of the entire left side, with loss of position sense and with astereognosis. Some scattered touch and pain points were elicitable and showed increased threshold, explosive reaction, long after-effect and wide radiation of the pain.

Most of the sensation, wherever elicited, was referred to the left upper arm and shoulder, but was not localized at all. The perception of the stimuli was inadequate quantitatively and qualitatively. Slight rubbing of the left sole, for example, was felt as an intense pain either "somewhere up in the thigh or shoulder," or without localization.

Pain sensation was slightly decreased over the right extremities also.

Chronaximetrically the rheobase was equally high but stable on both sides, the chronaxie high and increasing, with repeated stimuli on both sides, but much more on the left.

The patient's mental faculties were dulled by suffering and opiates. Her interests were limited to her pain and its relief, and she was insistent upon any type of operation which offered the slightest hope of alleviating her discomforts.

In our therapeutic considerations we were guided by our above-mentioned experience with major trigeminal neuralgia. If that assumption held true, blocking of the 5th nerve should in this case also relieve the pain in the face. On May 27, 1935, alcohol was injected into the left gasserian ganglion with immediate and complete relief of all pain and all paræsthesias in the three divisions of the 5th nerve, while the adjacent area of C2-3 became more painful than ever. Although the face was almost anæsthetic and analgesic before the alcohol injection, the patient complained of numbness after the injection.

Since interruption of the cranial nerve had proven so helpful in relieving pain, the next step was to try the effect of spinal anæsthesia. To our surprise this procedure, though effective on the right side, increased considerably the pain in the left leg for the time of its duration. The two experiments, of course, were not equivalent, as the sensitivity of the 5th nerve includes only part of the tactile sensation. The varying result may be explained in accordance with the experience that a lesion of Goll's and Burdach's tracts produced or increased pain, as demonstrated by Brown-Séquard [1].

Following this negative result we suggested a cordotomy. On July 3, 1935, the right anterolateral column was divided in the fifth cervical segment. At the same time, the second and third left posterior cervical roots were crushed. The cordotomy itself was unusually painful.

For about two weeks after operation the patient had gradually decreasing pains in the right arm, presumably from stretching of the posterior roots in

turning the cord. But the left side of the body and extremities were completely free from pain and dysæsthesia. Two days after the operation it was possible to cut down the daily dose of morphine from 9 to 2 gr. The patient left the hospital on July 16, 1935, no longer taking morphine, free from pain in her left side, and able to walk. This complete relief continued for another couple of months, when gradually some pain reappeared in the left shoulder and heel but not in the trunk. She remained free of morphine despite her discomfort.

It is well known that in cases of thalamic lesion with pain occurring in attacks, the paroxysm eventually may be elicited by stimulating the healthy side. Therefore, we were not surprised that the unilateral cordotomy was not permanently effective, and accordingly advised the referring physician to send the patient back for cordotomy of the opposite side whenever the pain again should become intolerable.

According to the patient's statement, it was not until about six months after the operation that the pain began to increase considerably.

At that time the alcohol injection of the left trigeminal nerve became ineffective. Late in February, 1936, her physician wrote that "the operation did her a great deal of good and her general condition is as good or better than before the operation."

The patient was readmitted on March 6, 1936, nine months after her first operation. She claimed that for the last four or five weeks the pain had increased rapidly although it was still not as bad as before the operation. The pain was localized in the left hand, shoulder, and heel, the rest of the arm and thigh being fairly free and the trunk completely pain-free. In the face, an area about two inches wide in front of the left ear was particularly sensitive to stimulation, pressure or draught. The pain had changed its character. The peculiar sensations of "hot lead" or "red lava" or "icy water" had disappeared. What was left was an indescribable "pure" burning, throbbing sensation, not an excruciating pain—sometimes absent for days, then again suddenly recurring. Such attacks often occurred during sleep and the patient awoke with pain.

The mental attitude of the patient had improved amazingly. In contradistinction to her behaviour previous to her first operation it was now possible to discuss with her different problems. She was anxious not to spend too much money and explained sensibly how difficult it was to make ends meet because of her long illness. In summary, it was the general opinion of the observers, as well as of the patient, that the discomforts were not nearly so great at this time as on the occasion of her previous admission.

Objectively, the sensibility was, with slight variations, about the same as before the cordotomy. Graphesthesia was now absent on both sides. Finger touch (not hairs up to 20 grm.) were felt all over the left side of the body but could not be localized. They had a disagreeable feeling tone on the face but not on the arm and leg. Stroking the sole was perceived as "tickling."

Pinching the skin was correctly localized from the left hand upward to the elbow. From there up to the shoulder it was referred to the fingers. Exactly the same held true for pin-prick except on the leg. On the thighs thorns of 8 grm./mm. were perceived but could not be identified, while pin-prick at the sole and ankle were correctly localized and somewhat sharp.

Pressure sense was normal on the whole right side and on the left side of the face with 50 to 70 mm. Hg. Pressure of 110 to 150 mm. Hg. "hurt" on the left arm: 200 mm. Hg. was felt over the left side of the chest; no pressure was felt on the left thigh but 230 mm. Hg. was felt over the left tibia.

Chronaximetrically the right side showed, as it did before cordotomy, normal and stable rheobases and slightly elevated chronaxie figures, increasing with repeated stimulation. On the left side 200 V were not perceived on the face and leg. At the left arm and hand rheobase was normal and stable, chronaxie considerably increased. With long ($\frac{1}{5}$ sec.) and repeated stimuli occasionally the sensation became disagreeable, eventually suddenly "pin-like," but not painful.

On March 10, 1936, a left-sided cordotomy was performed at the level of the first operation, resulting in analgesia of the right side up to the shoulder. The patient's immediate convalescence was somewhat stormy, partly as the result of her precarious kidney function (which barely kept her from uræmia) and partly as the result of unexplained sudden, wide fluctuations of her blood-pressure. This became stabilized at 150 to 180 systolic in a few days and the patient's condition improved.

On March 20, 1936, the left gasserian ganglion was reinjected with alcohol. During the injection the patient experienced a good deal of pain which stopped in a few seconds. Good relief was obtained.

At the time of her discharge the patient had a complete loss of pain and temperature sensation on the right side up to her shoulder and on the whole left side, with the exception of the heel, where deep pin-prick was painful. Subjectively, the patient complained mostly of this spot. It was the general opinion that she had very little severe pain.

As far as we could learn from the report of her family physician the patient's condition continued to improve for a short time and then became more or less stationary. At this time her physician wrote: "I think that she was relieved of a considerable amount of the pain by the two operations performed." On May 29, 1936, she rather rapidly became uræmic and died.

Discussion.

The main interest of this observation, in our opinion, consists in the opportunity to explore some problems of pain physiology in man with the exactness of an animal experiment.

Our starting point was the assumption that trigeminal neuralgia was due to peripheral stimulation of the 5th nerve in the presence of a thalamic lesion. In this particular case, where the pain was undoubt-

edly of thalamic origin, blocking of the peripheral nerve at the gasserian ganglion gave immediate and complete relief in the distribution of the 5th nerve. We feel, therefore, that this experience represents a further corroboration of our premise as far as trigeminal neuralgia is concerned. In addition, we would be inclined to link up also other forms of typical neuralgic pain with the "syndrome thalamique" although for the present time there is no proof of this point.

What is the mechanism of this central pain? Three theories are prevalent concerning the origin of thalamic pain. The oldest assumes that the lesion acts as a constant stimulus upon the pain-conveying elements in the optic thalamus. Head and Holmes [3], on the other hand, believed in the liberation of the thalamic pain apparatus by interruption of an inhibitory descending cortico-thalamic tract. A third theory, finally, is based on clinical experiences in lesions of Goll's and Burdach's tracts. The posterior columns convey what Foerster calls the "perceptive epicritic" system of sensibility, the neosensibility of Brouwer, comprising the kinesthetic, pressure and discriminating sense. Foerster [2] advanced the idea that with the destruction of these tracts the "affective" system in the anterolateral columns, the palæosensibility of Brouwer, became hypersensitive.

Foerster's hypothesis was confirmed by our experience. Spinal anæsthesia involving both the palæo- and neo-sensibility increased the pain in the anæsthetized area.

Interruption of the ipsilateral pain and temperature fibres by cordotomy relieved the pain due to a lesion in the region of the optic thalamus. Subsequent cordotomy of the opposite side improved the result. The pathologic-anatomical condition within the thalamus was, of course, not changed by either operation. What was changed was the afflux of peripheral pain and temperature stimuli. We have no proof that all pain fibres were destroyed. Foerster and others claim that a system of short internuncial fibres convey pain sensations in addition to the anterolateral tracts. However, the amount of afferent painful stimuli was definitely reduced. This experience supports the conception that in the presence of a thalamic lesion peripheral stimuli—possibly subliminal under normal conditions—become supraliminal and even painful. In other words, peripheral stimuli seem to be indispensable to produce central pain. Such peripheral stimuli seem for the most part to come from the portion of the body whose central representation is involved in the thalamic lesions. However, the convergence of all sensory stimuli (probably from both

sides of the body) on each optic thalamus provides the possibility of stimulation of any part of the body acting as a trigger mechanism for the pain. Consequently surgical interruption of the peripheral pathways from the painful extremities might still be followed by pain projected to this area. The theory that a continuous stimulation of the thalamic pain apparatus by a local process is essential should therefore be abandoned.

The sensory system—similar to the motor system—seems to follow the pattern of a brake machine. The activity of a lower circuit is always braked or regulated by a higher level. When this brake becomes loose, the phylogenetically older, lower system grows overactive. In the motor system this means increased motor reflex irritability; in the sensory arc increased sensitivity. The disorganization of the thalamic switchboard may further lead to an increase of the refractory period—to abnormal summation phenomena and to transformation of sensations (Gestaltwandel). Slight repeated touch stimuli suddenly produce very disagreeable pain or temperature sensation.

The mechanism of neuralgia pain suggests that a certain grade of excitation is required to pull the trigger of the paroxysm. We know to-day that the strength of a stimulus depends exclusively on the number of nerve fibres involved. Certainly not all fibres of a nerve have to be blocked to prevent a paroxysm. How far they have to be reduced relies mainly on the absence of summation phenomena which do not exist normally, but may appear with a thalamic lesion.

Clinical evidence suggests that a certain relation exists between the extent of the thalamic lesion and the number of afferent fibres which have to be interrupted to give full relief of pain. It is a common experience in retrogasserian neurotomy that in one patient pain subsides completely, although a considerable number of pain points are still demonstrable. In another patient a few omitted fibres may maintain severe pain in one or more divisions of the 5th nerve. The phenomenon of radiation of pain from one division of the trigeminal into the next may be part of the same problem.

In stressing the quantitative factor the importance of the exact situation of the lesion within the thalamus or in the thalamo-cortical system should not be neglected. It is well known that most of the smaller thalamic hæmorrhages leave the face free of pain. The trigeminal fibres end in a separate thalamic nucleus and do not become involved in the thalamic syndrome until the lesion is comparatively extensive. On the other hand, a growing granuloma of the optic

thalamus may for a considerable time simulate a simple trigeminal neuralgia until gradually the pain encroaches upon the extremities (C. Winkler [7]).

These considerations first of all bear on the spinal pain system with the optic thalamus as the regulating centre. Whether the release of the thalamus itself through the lesion of the superimposed striatum and of the cortical sensory centres yields a similar syndrome, as Head and Holmes suggested, or wherein it varies, is still open to discussion.

In conclusion, we gather from our observation (1) that thalamic pain is the result of two factors: (*a*) a lesion of the pain-damping system of the posterior spinal tracts within the optic thalamus, and of such mechanisms as prevent summation, amalgamation, after-effects, &c.; (*b*) continuous slight stimulation of the peripheral pain, &c., fibres. (2) Trigeminal neuralgia, and eventually other forms of typical neuralgia, seem to represent special forms of the thalamic syndrome in which the lesions are confined either to the end places of the trigeminal system or to the thalamic sensory arrangement of an extremity, &c. (3) Sufficiently extensive surgical interruption of the pain, and other fibres in the antero-lateral columns, leaving intact posterior roots, horns and tracts, eventually supplemented by blocking of the 5th nerve, seems to be a method of relieving these unbearable and up to now incurable central pains.

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COMPRESSION OF THE SPINAL CORD IN THE NEIGHBOURHOOD OF THE FORAMEN MAGNUM.

BY C. P. SYMONDS AND S. P. MEADOWS.

WITH A NOTE ON THE SURGICAL APPROACH,
BY JULIAN TAYLOR.

THE clinical picture which results from compression of the spinal cord at, or near, the level of the foramen magnum is not always easy of recognition. In particular the distinction from intramedullary disease (tumour or syringomyelia) may be difficult. Of the seven cases which we have to report, in one the compression was caused by an aneurysm of the right vertebral artery, in one by an atlanto-axial dislocation (probably of congenital origin) and in each of the other five by a benign tumour (endothelioma or neurofibroma). In all these cases the differential diagnosis from intramedullary tumour was for some time in doubt, and in only two instances was the correct diagnosis confidently made before operation. Three of the tumours were successfully removed by Mr. Julian Taylor with complete recovery.

There are on record many reports of comparable cases. In most of them, however, the clinical notes are incomplete, especially those which refer to the subjective and objective disturbances of sensation. Many writers have emphasized points of importance or interest in the clinical picture, but few have reviewed it as a whole.

The most important contributions to the subject which we have found are those of Elsberg [2], and Elsberg and Strauss [4]. Elsberg [2], in his monograph on spinal cord tumours, reported two cases of compression at the level in which we are interested, one from a dermoid cyst, the other from an aneurysm of the right vertebral artery. In reviewing cases of compression at a high cervical level—between the first and third segments—he laid stress upon the following points: Pain in the neck and occipital region is an important symptom and is increased on movement of the head. The patient is, therefore, apt to hold his head stiffly. Weakness first appears in the ipsilateral upper limb and is soon followed by subjective and objective sensory disturbances in the same limb. As weakness appears in the other limbs

it usually does so in a regular sequence, first affecting the ipsilateral lower limb, then the contralateral lower limb, and finally the contralateral upper limb.

Elsberg and Strauss [4] again emphasize the importance of pain and rigidity in the neck, and observe as a striking feature the occurrence of dissociation in the cutaneous sensory loss of syringomyelic type. They add that the complaint of cold in one or both lower limbs, usually in the contralateral limb, is a common subjective symptom, which they have only encountered in these high cervical tumours. They note also the occurrence of atrophy in the muscles of forearm and hand in cases of extramedullary tumour confined to the upper three cervical segments.

Most of these points are illustrated in the reports which we present.

Case 1.—*Endothelioma (psammoma), on the right lateral aspect of the cord extending above and below the foramen magnum.*

W. E., female, aged 57, came to one of us (C. P. S.) on March 5, 1934, on account of weakness in her right arm and leg. Her personal history contained the story of a doubtful pulmonary tuberculosis at the left apex, and an accident in 1929, when she was concussed and unconscious for over an hour, and afterwards she suffered from headaches for several months. The history of her present illness began in 1928, when she began to have an aching pain in the right suboccipital region. This persisted until June, 1933, when she became aware of a sensation of numbness over the same area.

In August, 1933, she noticed numbness in the thumb, middle and ring fingers of the right hand. This was soon followed by weakness of the right hand, and later of the whole right arm. At this time she noticed a hypersensitiveness in her right limbs. "Sometimes when I cut my finger nails on the right hand it's an intolerable stimulus: I feel I must draw away: there is the same sort of feeling in the right leg." About the same time the right leg began to drag and she was apt to trip on uneven ground. In February, 1934, the right suboccipital pain returned, and was aggravated by coughing or jolting. A feeling of stiffness in the neck developed together with a sensation of coldness along the ulnar border of the left arm and hand.

On examination she appeared in good general health and was an excellent witness.

Cranial nerves.—The left pupil was smaller than the right, and the palpebral fissure was narrower on the left than on the right (i.e. slight left cervical sympathetic palsy). The tongue was protruded slightly to the right, but there was no wasting or fibrillation. The functions of the other cranial nerves were normal.

Motor system.—There was a spastic right hemiparesis of moderate degree

considerably worse in the upper limb than in the lower, and slight wasting of the dorsal interossei of the right hand.

Sensation.—Pain and temperature sensibility was impaired over the left half of the body up to the second cervical segment. Pain was also much impaired over the upper cervical segments on the right side (fig. 1). Tactile sensibility was normal, even light stimuli being appreciated. There was no disturbance of vibration or postural sensibility.

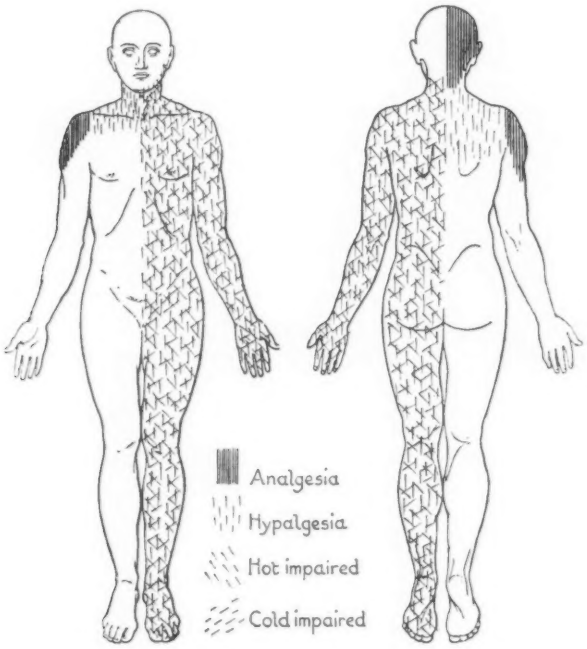

FIG. 1.—The sensory loss in Case 1.

Reflexes.—The tendon reflexes were increased in the right upper and lower extremities, the right abdominal reflexes were diminished, and both plantar responses were extensor. There was no disturbance of sphincter control. There was a slight dragging of the right leg in walking.

Spine.—There was a slight tenderness on pressure over the upper cervical spine, but no deformity. Movements of the cervical spine were unrestricted, except that rotation of the head to the left resulted in pain in the right side of the neck posteriorly.

Spinal fluid.—Lumbar puncture was performed on two occasions, in March and April, 1934. There was a quick and good rise in tho cerebrospinal fluid pressure on unilateral jugular compression on each occasion, and no

evidence of spinal block. The initial pressure was 155 mm. of cerebrospinal fluid which rose quickly to 270 mm. on right jugular compression, and fell quickly to 150 mm. on release of compression. The final pressure after removal of 5 c.c. was 105 mm. The cerebrospinal fluid contained one cell per c.mm. and 80 mg. total protein per 100 c.c. (60 mg. per cent. on the second occasion). There was no increase in globulin and the Wassermann reaction was negative.

FIG. 2.—Arrest of lipiodol in Case 1. True localization. Patient head downwards.

X-ray examination.—Stereoscopic views of the cervical spine showed no abnormality.

Cisternal puncture was attempted but no fluid was obtained. The tumour was presumably near the foramen magnum and extramedullary. 1 c.c. of heavy lipiodol was injected into the lumbar sac, and an X-ray taken with the patient head downward on a tilting table, showed the lipiodol held at the level of the atlas, though a few drops had passed through into the cranial cavity (fig. 2).

Operation.—Mr. Julian Taylor operated on April 17, 1934. The plan adopted was exposure of an area centred on the foramen magnum, necessitating an upper cervical laminectomy together with a limited craniotomy. On reflection of the dura mater, the proximal cervical cord was seen to be

displaced and rotated to the left by a lobulated mass lying to the right (fig. 3). The upper cervical posterior roots were seen coursing over the tumour. The roots and cord were freed from the tumour with some difficulty, and on release from these structures the tumour was found to be attached to the dura at the level of the foramen magnum. Division of this attachment enabled

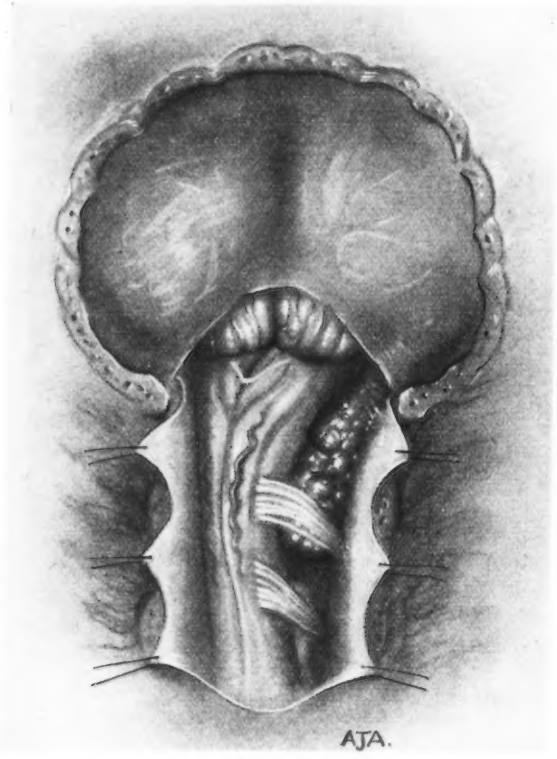

FIG. 3.—The tumour in Case 1, from a sketch made at the operation.

delivery of the tumour from its bed. The major portion of the tumour was situated in the posterior cranial fossa, while the smaller part extended down the spinal canal for a short distance.

Histological examination.—The tumour was a whitish, encapsulated lobulated, mass weighing 7 grm. and measuring 3·5 × 2·5 × 1·5 cm. Microscopical examination proved it to be a psammoma.

Post-operative history.—There was a considerable degree of post-operative weakness of the right arm, but this was only of temporary duration, and subsequent progress was steady.

Examined on February 28, 1935, ten months after her operation, she was able to walk two miles before any sensation of fatigue appeared in her right leg. She had normal use of her upper limbs, but after writing for a long time noticed occasional spasm of her right arm—a forward movement at the shoulder, with pronation at the wrist; also occasional "jerks" in her left hand. She was unable to distinguish between hot and cold water with her left lower limb, but could do so with the left upper limb. Elsewhere sensation appeared to her normal save for a constant feeling of coldness along the medial border of the left upper limb.

There was no trace of cervical sympathetic weakness. The right trapezius was weak and wasted and there was some limitation of passive movement at the right shoulder. There was slight weakness and spasticity of the right upper and lower limbs. Sensory examination showed an area of cutaneous analgesia roughly corresponding with the 4th and 5th cervical segments on the right. On the left there was loss of sensation to pain, heat and cold over the lower limb and trunk and upper limb up to the level of the 7th cervical segments, above which responses gradually became more accurate until, above the clavicle, they were normal.

The tendon reflexes in upper and lower limbs were brisker on the right than on the left side. The right plantar response was extensor, the left flexor.

Case 2.—Endothelioma on the right postero-lateral aspect of the cord, extending above and below the foramen magnum.

Mrs. S., aged 50, was referred to one of us (C. P. S.) on November 1, 1933. Between one and two years before the date of examination this patient began to suffer from pains at the back of the neck and head, subsequently radiating down the right arm. This was followed by tingling, weakness and stiffness of the right arm and hand. There was also some tingling in the left hand, and finally progressive weakness of both lower limbs, more especially of the right lower limb. There was no history of paræsthesiæ in the lower limbs and no sphincter disturbances.

Cranial nerves.—The pupils were irregular but reacted normally. The cranial nerves were otherwise normal.

Motor system.—There was a spastic weakness of all four limbs, more right than left, and equal in upper and lower limbs.

Sensation.—Tactile sensation was everywhere normal. Over the left limbs and trunk there was complete analgesia up to a poorly defined level at the juncture of the 2nd and 3rd cervical segments, except over the 2nd to 5th sacral segments where sensation to pin-prick was relatively unimpaired. On the right side there was hypalgesia of similar distribution. There was impairment both to heat and cold over the left trunk and limbs of the same distribution as the analgesia. Responses both to the hot and cold tests were variable and appreciation slow. There was no loss over the right trunk or limbs.

The sense of passive movement was perfect in all digits of both feet and

left hand; in the right hand there was some uncertainty of response, but no gross defect.

Appreciation of vibration was completely lost over the whole right upper limb from fingers to acromion process and clavicle, inclusive. Elsewhere appreciation was normal save over the iliac crests, but the patient being extremely stout, the last observation was considered to have no clinical importance.

Reflexes.—The triceps, biceps, supinator, knee and ankle jerks were all increased on the right side. Ankle clonus was present on the right. All abdominal reflexes were absent. The right plantar response was extensor, the left was sometimes absent, sometimes extensor. There was no impairment of sphincter control.

Gait was spastic and weak, but the patient was able to walk unaided.

FIG. 4.—Arrest of lipiodol in Case 2. False localization. Patient head downwards.

Spine.—The patient held her neck somewhat rigidly, but was able to perform all movements on command except extreme flexion of the neck. Passive movement in this direction was also limited. The upper cervical spines were tender on pressure.

Spinal fluid.—The initial pressure was 75 mm. of water. Compression of the left jugular vein gave a rise to 170 mm.; of both jugulars, a rise to 220 mm. On each occasion both rise and fall were slow. The fluid was clear and contained no cells. The protein was 100 mg. per cent. The Wassermann reaction was negative.

X-ray examination.—Stereoscopic views of the cervical spine showed no abnormality. An attempt was made at cisternal puncture, but failed. Subsequently, 2 c.c. of lipiodol were injected by lumbar puncture. The patient was gradually tilted to an angle of 80° and the shadow of the lipiodol observed. It

flowed gradually to the level of the 6th cervical vertebra, when it became arrested, and no further movement was observed at the end of ten minutes (fig. 4).

Operation.—Mr. Julian Taylor operated on December 12, 1933. The spinal cord was exposed by removal of the 3rd to the 6th laminæ. No abnormality was observed. The exploration was carried higher by the removal of the arches of axis and atlas, and the tumour was then discovered lying upon the right postero-lateral surface of the cord just below the foramen magnum, and extending upwards to a point just below the skull. It was entirely removed piecemeal.

Histological examination.—Dr. Greenfield reported the tumour to be a cellular endothelioma with large whorls of fleshy cells centred on a small knot of hyalinized connective tissue often partially calcified.

Post-operative history.—No complete examination was made until five weeks after operation. The patient was sensitive and resented disturbance. There was no loss of sphincter control in the post-operative phase, nor any trigeminal anæsthesia or nystagmus. Motor and sensory function in the right upper limb showed improvement within the first week.

On January 20, 1934, there was no abnormality of the cranial nerves.

Weakness and spasticity were apparent in all four limbs. Weakness was greater on the right than the left, and most evident in the small muscles of the right hand, and extension of right wrist and elbow. In addition there was definite wasting of the small muscles of the right hand.

Pin-prick was appreciated normally and equally in both lower limbs and also over the trunk up to about the 4th thoracic segment. Above this up to the clavicle, there was relative analgesia on the left, and above this again a zone of intense over-reaction with raised threshold up to and including the second cervical segment. No defect of postural or vibration senses could be discovered in any part. The reflexes showed no important change from before operation. The patient walked quite well unsupported.

She attended by request for examination by one of us (S. P. M.) on December 4, 1935, that is, nearly two years after the operation. She did not complain of any disabilities. She was able to walk well and perform her ordinary household duties which included cooking. She had, however, aching pains at the back of the head and neck and in the right shoulder.

On examination there was no defect of the cranial nerve functions; no defect of sensation to touch, pin-prick, heat, cold, postural tests or vibration, in trunk or limbs; no weakness, wasting or dystonia. The tendon-jerks in upper and lower limbs were brisk and equal, all abdominal reflexes present and equal, plantar responses both flexor, though left not so easily obtained as right. Sphincter control and gait were normal.

Case 3.—Endothelioma on the right antero-lateral aspect of the cord extending above and below the foramen magnum.

Mrs. H. L. B., aged 42, was referred to one of us (C. P. S.) on October 25,

1935, on account of weakness and numbness in her limbs. Her family and personal history contained nothing relevant. She had been married sixteen years, but there had been no pregnancy. The story of the present illness began two years previously, when she noticed that whenever she was in "a tight jam" (e.g., if she was driving in a car and had a narrow escape from accident) a momentary tingling sensation would run up her right arm from fingers to shoulder. At about the same time she began to experience occasional shooting pains at the back of her head on the right side, which were ascribed to neuritis. As time progressed the right hand became progressively more dead and useless. The pain at the back of the head recurred and spread across her neck and shoulders, first on the right side and then on the left. During the past month she had noticed a numbness in the left little finger which spread radially to the other digits. Later the numbness spread down the left side of her body and involved the left lower limb, in which it was associated with a pain "like sciatica." At the same time both lower limbs became weak.

On examination she proved an intelligent and co-operative patient.

Cranial nerves.—These showed no abnormality, save for a slight right-sided enophthalmos. There was no nystagmus, no impairment of sensation in the right trigeminal field, and no weakness of right sterno-mastoid or trapezius.

Motor system.—In the upper limbs there was a severe degree of weakness with moderate spasticity, greater in the right than the left. Both lower limbs were slightly weak and spastic, the right again being more affected than the left. No clonus was obtained at wrists, fingers or ankles.

Sensation.—There was no gross defect to light contact, but over the left trunk and limbs, from the second cervical segment downwards, occasional stimuli were missed by contrast with uniformly correct appreciation on the right.

Pin-prick over the 2nd to 4th cervical segments on the right was less vividly appreciated than over the remainder of that side of the body. On the left side there was complete analgesia below the trigeminal field, with the exception that within an area corresponding with the 6th to the 11th thoracic segments the prick was occasionally felt, and, if felt, was associated with marked flinching and an exclamation of pain. At one examination islands of relatively normal sensibility were found in the lower sacral segments. The upper level of cutaneous analgesia at its boundary with the trigeminal field was very sharply defined.

Over the 2nd to 4th cervical segments on the right, heat and cold were less vividly appreciated than on the rest of that side of the body.

On the left there was loss of all sensation to heat and cold below the trigeminal field down to and including the 5th thoracic segment. Below this, in a zone covered by the 6th to 11th thoracic segment an anomalous state existed. There was no recognition of heat, even if of painful degree. The cold tube, however, was invariably called hot with flinching and an exclamation of pain. Below this again, from the 12th thoracic to 1st sacral segments, there was loss of all sensation to both heat and cold. Over the remaining sacral segments heat was appreciated as such, whereas the cold tube was called warm.

The sense of passive movements was completely lost in all digits of both hands. In the left toes the slightest movements were immediately and correctly appreciated. In the right toes small movements were slowly, but usually correctly, appreciated: with larger movements there was no difficulty.

Vibration sense was completely lost over the trunk and upper limbs, including the clavicles and iliac crests. In the lower limbs it was lost on the right, but present on the left when the tuning fork was applied to internal and external malleoli, tibia and patella.

Reflexes.—The triceps, biceps and supinator jerks were abnormally brisk, more so on the right than the left. The abdominal reflexes were absent. The knee and ankle jerks were brisk, the right more so than the left, Both plantar responses were extensor. A pin dragged across the skin over the left anterior thoracic wall at the level of the axilli provoked a reflex spasm of the corresponding upper limb, comprising adduction at the shoulder, flexion at the elbow, and pronation and flexion at the wrist. No such reflex was present on the right. There was no disturbance of sphincter control.

Gait was spastic and unsteady, but the disability was much less in the lower than in the upper limbs.

Spine.—Voluntary movements of the head and neck were carried out to command without absolute restriction, but the patient preferred to turn head and trunk together in rotation, especially when rotating to the right. Passive movements were unrestricted, save that full rotation, especially to the right, gave rise to an uncomfortable sensation of tightness, referred on each occasion to both sides of the neck and the back of the head.

No tenderness of the cervical spines could be detected on palpation.

Spinal fluid.—The initial pressure was 40 mm. of water (about $\frac{1}{2}$ c.c. was lost on account of a sticking tap before the pressure reading was taken). Compression of the left jugular vein gave no rise of pressure. Compression of the right jugular gave a slow rise to 80 with a more rapid fall on release. Compression of both jugulars gave the same result as compression of the right alone. All observations were repeated. The residual pressure after the removal of 5 c.c. of fluid was 5 mm. of water. Examination of the fluid (Dr. J. G. Greenfield) showed it to be clear and colourless. It contained 2·5 cells per c.mm., small and medium mononuclears: total protein was 200 mgm. per cent.: Nonne-Apelt and Pandy tests were positive: gold sol. 0000122110: Wassermann reaction was negative.

X-ray examinations.—Stereoscopic views of the cervical spine showed no abnormality. On the third day after the initial lumbar puncture 2·5 c.c. of lipiodol were injected by lumbar puncture. The patient was then tilted to an angle of 20° from the vertical plane head downwards and the shadow of the lipiodol observed. It was seen at the site of injection, gradually becoming elongated, but showed no movement at the end of several minutes.

Operation.—Mr. Julian Taylor operated on November 4, 1935. At the level of the foramen magnum the posterior aspect of the cord appeared pale and slightly swollen. The apparent swelling proved to be due to slight

backward displacement by a tough encapsuled tumour lying upon the right anterolateral surface of the cord in close proximity to the emerging fibres of the spinal accessory nerve. The tumour was completely removed at the end of an operation lasting two hours.

Histological examination (Dr. J. G. Greenfield).—A firm, rather brown, tumour, roughly pyriform in shape and weighing 6 grm. Histologically the tumour is an endothelioma composed of fairly fleshy cells in small whorls and larger masses which are separated by very thick trabeculæ of collagen, in which the vessels run. Although in many places collagen preponderates over tumour tissue, there is no tendency to the formation of hyaline knots in the centres of the whorls.

Post-operative history.—The patient made a good recovery from the effects of the operation with no disturbance of sphincter control. On November 12 her general condition was good and allowed of a fairly full examination (S. P. M.). As a result of the operation, new physical signs had developed as follows: Cervical sympathetic weakness on the right was more evident, i.e. ptosis and miosis in addition to enophthalmos. Nystagmus was present on deviation of the eyes in either direction in the horizontal plane, being more marked and coarser to the left. There was also an irregular fine nystagmus on upward deviation. The right corneal reflex was abolished, the left remaining brisk. There was analgesia over the whole right trigeminal field, the loss affecting all divisions equally and being strictly confined to the parts supplied by the 5th nerve. There was no loss of sensation to cotton-wool. The motor functions of right trigeminal were unaffected. There was paralysis of right sterno-mastoid and trapezius. The other cranial nerves were unaffected.

The cutaneous sensory loss over trunk and limbs remained unchanged. There was no loss of sensation to cotton-wool. Posterior column function already showed improvement; postural sense was grossly impaired in the right fingers, moderately so in the left, slightly impaired in the right toes, normal in the left. Appreciation of vibration was much impaired below the right elbow, but not as much impaired as might have been expected from the degree of postural loss. Over the left upper limb vibration was normally appreciated. The disturbance of motor function in the limbs and of the deep and superficial reflexes remained as before operation.

On November 30 a more complete examination was possible (C. P. S.). The patient now complained that when she was tired reading was difficult, but became easier if she closed one eye. No diplopia could be elicited. Nystagmus was now evoked only on deviation to the left, and was more marked in the left eye. The cranial nerves otherwise showed no change. Over the left trunk and limbs pin-prick was appreciated as such, but was said to be less sharp than on the right and there was no flinching reaction. To the hot and cold tubes over the same distribution the response as a rule was, "I'm not sure"; sometimes, "Hot [or cold] I think," and then generally correct. Over a zone conforming to the left 6th to 11th thoracic segments, although heat and cold were not distinguished, at contact with the cold tube she flinched

and said, "It makes me jump." She was unable to explain this sensation further. This response was invariable. There was no sensation of pain or flinching to pin-prick in this zone. The functions of the posterior columns showed further improvement; postural sense was normal in both lower limbs and in the left upper limb. In the right upper limb the following observations were made:—

Fingers and wrist: response slower than on the left with a good many mistakes.

Elbow: Response much slower than on the left, occasionally correct, but more often "not sure."

Shoulder: Grossly defective. ("I can't tell at all.")

Vibration was well and equally appreciated on the two sides of the body on the dorsa of the feet, tibiæ, iliac crests, lower costal margins, fingers (all digits separately), wrists, elbows and clavicles. On the right acromion process, however, vibration was constantly less well appreciated than on the left; at a low range of excursion of the tuning fork vibration was not felt on the right ("only heard"), but normally appreciated on the left.

There was a great improvement of motor function. The right upper limb was slightly spastic and generally weak, but there was no marked degree of weakness except at the shoulder and in the hand. These was slight spasticity of the right lower limb and a just appreciable weakness of all flexor movements as compared with the left.

At this stage, however, a new symptom had appeared in the shape of wasting in the intrinsic muscles of the right hand. The thenar eminence was flattened and, with the hand lying palm upwards, the thumb fell back into line with the fingers. The interosseous spaces on the back of the hand showed as deep furrows. There was the beginning of a *main en griffe*. All movements were correspondingly weak. The deep and superficial reflexes showed no important change.

On January 6, 1936, the patient was again examined (C. P. S.). She had now been on her feet for a month and was able to do most things with her hands, the right being still the stronger. She was able to write without much difficulty. Her only complaints were that she still had difficulty with vision, having to close one eye for detailed work, and that on waking in the morning she felt giddy and sick, and, if she took a solid breakfast, often vomited.

The cervical sympathetic palsy, nystagmus and sensory loss over right face were present as before. The right corneal reflex was present and equal with the left. The right sternomastoid and trapezius, though weak, were contracting well.

The cutaneous sensory defect on the left had altered slightly. Its upper limit had receded and was less well defined. Analgesia was complete up to and including the 7th cervical segment. Above this it was incomplete and shaded off gradually to normal sensation at the upper level of the 3rd cervical segment. The loss to heat and cold was complete up to and including the 5th cervical segment and shaded off to normal at the level of 3rd cervical segment.

On this occasion, over the areas where discrimination between heat and cold was lost, the patient showed a tendency whenever she guessed to call all stimuli "warm." The zone of flinching to cold between the 6th and 11th thoracic segments remained as before.

There was nowhere any defect of postural or vibration sense. Wasting and weakness of the right hand were still evident, though improved. Apart from this, there was little weakness anywhere, though all four limbs were a little spastic, more so on the right than the left.

All the tendon-jerks were brisk, those of the upper limbs exceptionally so, but there was equality between the two sides. The abdominal reflexes were absent on the right, present on the left; the right plantar response extensor, the left flexor.

In walking, the patient showed an inclination of occiput to right shoulder, and tended to circumduct the right lower limb.

Case 4.—*Neurofibroma on the anterior aspect of the cord mainly below the foramen magnum, but with a small protusion through and above it.*

Mrs. C. N., aged 38, was admitted to the National Hospital, Queen Square, on August 3, 1934, under the care of Dr. James Collier, and was examined by one of us (S. P. M.).

The patient was one of fifteen children, of whom six were living at the time of the patient's admission to hospital. She had been married seventeen years, and had six healthy children, including one set of twins. She had been a strong healthy woman until the onset of the present illness.

Symptoms commenced in 1930, four years previous to admission to hospital, when the patient was pregnant. She then noticed a feeling of numbness and tingling in the right hand which slowly became weak. She also had œdema of the legs at this time, but was told that this would clear up after the confinement. The numbness slowly spread from the right hand up to the elbow, but no further.

In 1932, two years before admission, weakness and dragging of the right leg became manifest. Following this her neck became weak, so that her head fell forwards, and maintenance of the erect attitude was impossible. The right arm and leg and the neck became progressively weaker.

Early in 1933 she was admitted to a hospital for a month, and at this time the weakness of her neck improved and she could walk with a slight limp. In November, 1933, nine months before admission, she became progressively worse, and her neck, right arm and right leg were much weaker. Four months previous to admission the left leg also became weak, and finally the weakness extended to the left arm. She was by this time unable to feed herself, and had difficulty in breathing, coughing and sneezing. There was no difficulty in speaking and her voice remained unchanged. Nor had there been any dysphagia.

There had been little pain, though she had considerable "soreness" of the back of her head during the latter few months, and her head felt tight, "as if in

a vice." Turning the head produced pain in the neck, more particularly if she turned her face to the right. She stated that she was still able to feel in the paralysed limbs, and could still appreciate touch or the warmth of a hot bottle. Her legs and feet were always cold.

There had been no disturbance of micturition, but she had been subject to constipation for a few months since being confined to bed.

On examination in August, 1934, the patient lay on her side, with her head slightly extended to assist respiration. There was marked respiratory distress, the respiratory rate being 30 per minute. She was breathing almost solely with the sternomastoids and platysma, and could only talk in gasps.

Cranial nerves.—The right palpebral fissure was smaller than the left, and on one occasion there was a fine quick horizontal nystagmus on lateral deviation. The cranial nerves showed no other abnormality.

Motor system.—There was a severe degree of weakness in all four limbs with moderate spasticity. The upper limbs were equally weak, but the left lower limb was weaker than the right. There was generalized muscular wasting of both upper limbs.

The neck and trunk musculature was also very weak. Both sternomastoids contracted during respiration, but both were weak on active rotation of the head. The patient was unable to lift the head from the pillow. Extension of the neck was feeble, but slightly stronger than flexion. She was able to hold the head erect if she was supported in a sitting position. The patient was unable to sit up without assistance, and the abdominal musculature was very flaccid, but contracted feebly on coughing or straining. The intercostal muscles were paralysed and the epigastrium retracted on inspiration, suggesting diaphragmatic paralysis.

Sensation.—Owing to her general state, the patient was a poor witness. On admission there was a band of impairment to pin-prick on the right side from the 1st dorsal to the 1st lumbar root areas. Vibration was lost in the left lower limb, and there was loss of postural sense in both lower limbs.

Later examination revealed a sensory level to pin-prick at the junction of the 2nd cervical and trigeminal sensory areas in the right side, with impairment of pin-prick over the left side of the body up to the neck.

Tactile sensibility, tested with cotton-wool, was very little affected.

The appreciation of vibration was much impaired in all four limbs, and in the trunk up to the cervical spine. The sense of passive movements was lost in the fingers of both hands and in both great toes.

Reflexes.—The arm jerks, knee jerks and ankle jerks were exaggerated in all four limbs, and there was knee and ankle clonus. The abdominal reflexes were absent, and both plantar responses were extensor. There was no disturbance of sphincter control.

Spine.—The spine of the axis was very tender on pressure, and there was much pain in this region when the head was moved from side to side. There was no deformity of the cervical spine.

Spinal fluid.—Lumbar puncture showed an initial cerebrospinal fluid pressure of 128 mm. of water, rising to 148 mm. on right jugular compression. There was a steady, but not quick, rise on bilateral jugular compression to 210 mm., and a more rapid fall to the initial pressure on release. After removal of 5 c.c. of fluid, the pressure fell to 20 mm., rising to 48 mm., when bilateral jugular compression was repeated.

Examination of the cerebrospinal fluid (Dr. J. G. Greenfield) showed it to be clear and colourless, with 5·5 cells per c.mm: total protein 200 mg. per cent.; Nonne-Apelt and Pandy tests strongly positive; gold sol, 0000012100; Wassermann reaction was negative.

X-ray examination.—Lateral and anteroposterior X-rays of the cervical spine showed no abnormality.

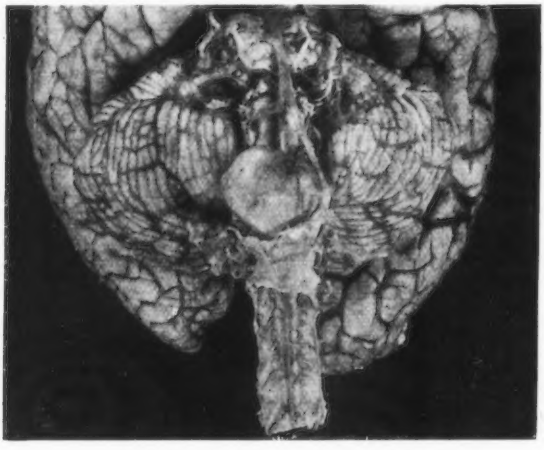

FIG. 5.—The tumour in Case 4.

Through the kindness of Dr. Collier we were able to examine the patient together and were of opinion that the case was one of extramedullary tumour just below or at the level of the foramen magnum.

Operation.—Mr. Julian Taylor operated on September 4, 1934. The exposure described in Case 1 was made, but the appearances on opening the dura were very different. The lower part of the medulla and upper part of the spinal cord presented what appeared to be three spheroidal prominences, giving the impression of some intramedullary change, possibly with cyst formation. On account of the precarious state of the patient, together with respiratory difficulty, it was considered unjustifiable to divide the nerve roots in order to facilitate exposure of the front of the cord, especially as the appearances described seemed to be indicative of the pressure of an intramedullary tumour. Further intervention being deemed inadvisable the wound was closed.

The patient died later in the same day. Post-mortem examination (Dr. J. N. Cumings) revealed a large tumour lying anterior to the medulla, part of which was extruded through the dura, forming a dumb-bell tumour (fig. 5). It was about 1 in. long and $\frac{3}{4}$ in. wide and felt moderately soft. A small portion, about a third of the tumour, protruded through the foramen magnum, which had been enlarged. The first three cervical segments appeared a little larger than usual.

Histological examination (Dr. J. G. Greenfield).—The tumour is oval, smooth and fleshy. It is a neurofibroma with many beautiful palisaded whorls. The main part of the tumour is fleshy with oat-shaped cells. The nuclei vary considerably in size, but all are rather vesicular in type. There is considerably more collagen in the whorled palisade areas than elsewhere.

Case 5.—Separation of the odontoid process with compression of the cord.

D. A., male, aged 47, labourer, was referred to one of us with the complaint of weakness of the right arm and leg, and subsequently admitted to the National Hospital, Queen Square. In his past history the only episode of possible relevance was an accident two years previously. He was struck by a running trolley on the back of the right shoulder and arm, was off work for a week, and on light work for several months. Eighteen months before admission he noticed weakness in the right forearm and hand. At about the same time he began to have a dull aching pain in the depth of the forearm, and an occasional prickly numbness along the medial side of the hand and medial three fingers. These symptoms became progressively worse until, at the end of six months, the weakness of his arm caused him to leave his work. Shortly after this, his right leg began to drag in walking. For a year he had had difficulty in starting micturition, and was unable to control a loose motion.

For three months he had complained of pain in the back of the neck and head. This was described as a shell of pain clapped on to his head and was aggravated by stooping.

On examination the cranial nerves showed no abnormality.

Motor system.—The upper limbs presented a moderate degree of spasticity, considerably greater in the right than in the left. Associated with this was weakness of upper neuron type, severe in the right limb, especially in dorsiflexion of the wrist, slight in the left. Both lower limbs were a little spastic, and there was slight weakness of the right limb in movements of flexion.

Sensation.—There was no gross defect of tactile sensation, but over the 2nd to 4th cervical segments light stimuli were occasionally missed. Over the 2nd to 4th cervical segments on both sides sensation to pin-prick was impaired. There was imperfect discrimination of heat from cold over the whole of the left trunk and limbs from the 2nd cervical segment downwards.

The sense of passive movement was defective in the right thumb, elsewhere

normal. The appreciation of vibration was completely lost over right trunk and limbs up to and including the acromium process. On the left it was lost in the lower limb up to and including the iliac crest, but was appreciated over the trunk and upper limb.

Reflexes.—The triceps, biceps and supinator jerks on both sides were very brisk. A scratch with a pin anywhere within the territory of the 4th cervical to 6th thoracic segments provoked a strong reflex movement in the upper limb of the same side taking the form of flexion at the elbow and slight abduction at the shoulder. The abdominal reflexes were absent. The knee-jerk on both sides was very brisk: the right ankle-jerk brisker than the left. Patellar clonus was present on both sides, ankle clonus on the right. Both plantar responses were extensor. There was difficulty in starting micturition, and imperfect control of defæcation after a purge.

Walking was quick, but with apparent effort, and slight dragging of the right leg.

Spine.—The 2nd cervical spine was unduly prominent and a little tender on pressure. There was no limitation of movement or rigidity in the neck.

Spinal fluid.—The initial pressure was 85 mm. of water. Right jugular compression gave a prompt rise to 230 with prompt fall on release. Left jugular compression gave the same results. The residual pressure after removal of 5 c.c. was 45 mm.

Examination of the fluid (Dr. Greenfield) showed it to be clear and colourless. It contained 1 cell per c.mm; total protein 35 mg. per cent.; Nonne-Apelt and Pandy tests were negative; gold sol no change; Wassermann reaction negative.

X-ray examination of the cervical spine showed no abnormality. 2 c.c. of lipiodol was injected intrathecally in the lumbar region and the patient examined on the tilting table. When the patient was tilted head downwards the flow of the lipiodol was very slow. Eventually the greater part of it was arrested at the level of the upper border of the 5th cervical vertebra, but some passed on and entered the skull.

Operation.—Mr. Julian Taylor operated on January 29, 1935. When the cord was exposed it was seen to be pushed rather acutely backwards at the level of the junction between atlas and axis, and a bony projection into the spinal canal was felt at this level. This was thought at the time to be an ossified chondroma, for it was very hard and could not be incised. The patient died from respiratory failure within forty-eight hours from the time of operation.

Post-mortem (Dr. Greenfield).—The cord was found to be curved sharply backwards (concavity forwards) at the level of the body of the axis. The head was unduly movable on the neck between the atlas and the axis and it was clear that the odontoid process of the axis was not attached to its body, the only connection between the body of the axis and the vertebra above it being two fibrous strands which were stretched to about a quarter of an inch in length. The upper surface of the body of the axis was rounded in conformity

with its articular surfaces which were very large. The atlas vertebra was normal and contained in its ring the odontoid process of the axis, which had an anterior articular facet, corresponding with a facet on the back of the anterior ring of the atlas, and a plate of fibro-cartilage on its lower surface. Professor T. B. Johnstone, who examined the specimen, considered the abnormality to be of congenital origin. The cord at this level was definitely compressed and thinned.

Case 6.—*Aneurysm of the right vertebral artery.*

R. F., electrician, aged 49, was admitted to the National Hospital, Queen Square, under the care of one of us (C. P. S.) on November 28, 1935, complaining of numbness and weakness of the right arm and dragging of the right leg.

There was nothing relevant in his family or past history.

The first symptom which might be connected with his present illness was a bout of hiccoughing eighteen months before admission, which had lasted on and off for ten days and had recurred occasionally during the succeeding three months.

Fourteen months before admission he first had pain in the right shoulder and tingling in the upper arm which gradually spread to involve the whole limb, including the thumb and fingers. At about the same time he experienced occasional giddiness on exertion—for instance running for a bus. Objects would momentarily seem to revolve in a clockwise direction. After he had stood still for a moment or two the symptom would disappear. All these symptoms cleared up and he was well for five months. Three months before admission the pain in the right shoulder recurred, followed by the tingling as before. The right hand and fore-arm became numb and stiff, and six weeks before admission he was unable to hold a pen. There was also recurrence of the giddiness. Subsequently he experienced stiffness and numbness of the left hand and fingers; the numbness began in the little and ring fingers and spread slowly up the ulnar side of the fore-arm to the elbow. About the same time he noticed dragging of the right foot, and within a week found himself unable to walk without support. At this time also he noticed on walking a tight feeling around his trunk at the level of the umbilicus "as if someone had tied a rope belt" round him. Subsequently the left leg became numb and stiff and he complained of some stiffness in the neck.

Cranial nerves.—At rest there was a continuous vertical nystagmus which was evident also on lateral deviation in the eyes in either direction and on downward deviation, but absent on upward movement. This nystagmus had a range of about 1 mm. and a frequency of about 2 per sec. Associated with the vertical movement was a slight anti-clockwise element. The corneal reflex was sluggish on both sides, more so on the right. Over the right trigeminal field there was slight hypalgesia and thermohypæsthesia, rather more marked peripherally than centrally, and in the second and third divisions more than the first. On phonation the pharyngeal wall moved slightly to the left. There was slight wasting and weakness of right sternomastoid and trapezius. The

right half of the tongue was wasted, and it was protruded a little to the right. Fine fibrillation was constant in its right half and occasionally in the left.

Motor System.—There was no spasticity of the upper limbs, but the right showed weakness of pyramidal type and distribution. There was also slight wasting of the muscles of the right thenar eminence and dorsal interossei.

There was clinical evidence (absent Litten's sign) of paralysis of the right half of the diaphragm, confirmed by X-ray screening. The lower limbs were not spastic, but the right was weak.

Sensation.—There was no gross defect to cotton wool, but a relative defect over the right, 2nd and part of the 3rd cervical segments, and on the left hand and fore-arm and the whole lower limb with the exception of the back of the thigh and buttock.

There was complete analgesia over the upper and outer aspects of the left upper limb (roughly the territory of 5th and 6th cervical segments) and the antero-external aspect of the left leg (roughly the territory of the 5th lumbar segment). From the analgesic areas hypalgesia extended over the whole of the left upper limb on to the neck and trunk to include the 2nd cervical segment above and the 4th thoracic below. In the lower limb hypalgesia was evident up to the 2nd lumbar and down to the 2nd sacral segments, but was less than in the upper limb.

The areas of loss and impairment to heat and cold corresponded closely with those for pain. There was no dissociation between heat and cold.

The sense of passive movement was absent in fingers, wrist, elbows and shoulders of both upper limbs, but normal in the lower limbs.

Appreciation of vibration was nowhere lost, but was markedly impaired in the right upper limb up to and including the clavicle and, by comparison with the lower limbs, impaired in the left upper limb.

Reflexes.—The triceps, biceps and supinator, knee and ankle jerks were all brisker on the right than the left. The abdominal reflexes were absent. The plantar responses were extensor. There was no defect of sphincter control. The patient could walk only with support, dragging the right leg.

Spine.—The head was carried stiffly, but there was no limitation of movement nor any tenderness or deformity of the cervical vertebræ.

Spinal fluid.—The initial pressure was 160 mm. of water, with free rise and fall on compression of either jugular vein, the heights reached being 300 mm. on compression of the right jugular, 280 mm. on compression of the left. The fluid was clear and colourless. It contained no cells and 60 mg. per cent. of protein. The gold sol showed no change. The Wassermann reaction was negative.

X-ray examination.—X-rays of the cervical spine showed no abnormality. No attempt was made at lipiodal injection.

Operation.—Mr. Julian Taylor operated on December 20, 1935. A large, rounded, oval, dark tumour mass was found lying upon the right posterolateral aspect of the medulla. The main mass was within the cranial cavity, but the lower end extended through the foramen magnum and obscured the cord down

to the level of origin of the first cervical root. Attempt at removal led to severe hæmorrhage and had to be abandoned. Death ensued a few hours later. At post-mortem the tumour proved to be an aneurysm (presumably congenital) of the right vertebral artery.

Case 7.—Endothelioma on the left anterolateral aspect of the cord extending above and below the foramen magnum.

Miss T., aged 43, was referred to one of us (C. P. S.) on March 16, 1936. She complained that for the past three years she had had pain at the back of her head. This was bilateral, suboccipital, and of a throbbing character, with an occasional shooting pain radiating forward into either temple. It was always more severe at night and in the early morning, usually wearing off before 10 a.m. It was worse at her periods. In the morning there was a feeling of pressure upon her head, as if there was something loose inside it. At all times she was subject to discomfort on movement of her head, especially when bending forwards. In the past fortnight her left hand had felt cold, and she had not been able to feel things so well with it. There had also been numbness in the left thumb.

She had always been of a nervous disposition, but though she was clearly of a psychoneurotic personality there was sufficient in her story to arouse the suspicion of a high cervical tumour. A careful examination was therefore made with this suspicion in view, but no abnormal physical signs could be found.

She was next seen on December 17, 1936, when her main complaint was still of pain at the back of her head, which was aggravated by bending forward, by any physical effort, by coughing or sneezing, and especially by straining at stool. She complained also of numbness and a stinging sensation in the back of her head, and of painful stiffness in her shoulders and neck. Her hands and arms felt numb and stinging, the hands swollen and heavy. The first sensation of numbness in the right hand had appeared in October. About the same time she began to have a continuous sensation around her neck, just above the Adam's apple, as if she were wearing a tight collar. Quite recently she had had a sensation of coldness around her right knee.

Again a full examination was negative.

She was admitted to the National Hospital, Queen Square, on January 8, 1937. The Resident Medical Officer, Dr. Smyth, noted that the tendon-jerks in the upper limbs were abnormally brisk on both sides, and that full flexion of the head caused her slight pain, but could find no other abnormality. Stereoscopic X-rays of the cervical spine revealed no abnormality. Lumbar puncture on January 18, 1937, showed a pressure of 85 mm. with rises to 170 mm. on right, 150 mm. on left, and 250 mm. on bilateral jugular compression. The rise and fall of pressure on each occasion were a little slow.

The spinal fluid was slightly yellow, contained no cells, but the total protein was 1,200 mg. per cent.: Nonne-Apelt and Pandy tests were strongly positive: gold sol curve was 0000000210. The Wassermann reaction was

negative in blood and spinal fluid. Following the lumbar puncture, she complained of continuous and severe pain in the nape of the neck.

Examination on January 21 revealed: on the right slight ptosis, enophthalmos and myosis, and inconstant nystagmus to the left. Both upper limbs were generally weak, but not spastic. Diaphragmatic movement on both sides was poor. The lower limbs showed no weakness.

There was no loss of tactile sensation, but a definite hypalgesia over the second to 4th cervical segments on both sides. Sense of passive movement was lost at all joints of both upper limbs, preserved but impaired in the lower imbs.

Vibration was not appreciated over the clavicles, acromion processes, elbows and wrists on both sides, but faintly appreciated over the fingers, ribs, iliac crests and lower limbs.

The tendon-jerks in all four limbs were abnormally brisk and equal on the two sides, the abdominal reflexes were absent, and both plantar responses were extensor. Sphincter control was unimpaired.

Operation.—Mr. Julian Taylor operated on January 23. On rotating the cord, he discovered an endothelioma the size of a large walnut attached to the dura upon the left antero-lateral aspect of the cord. About one-fourth of the tumour extended above the rim of the foramen magnum. The patient rallied well from the operation, and was comfortable next day, but died suddenly from respiratory failure twenty-four hours after operation.

Post-mortem examination showed the tumour to have been completely removed.

Discussion.

Having described our cases in detail, we propose to discuss the symptoms of the group as a whole under the several headings already used.

In Cases 1 to 4 and in Case 7, the level of maximal compression was below the foramen magnum, though in each case a part of the tumour extended above it. In Case 5 the level of compression was at the lower border of the atlas. In Case 6 the compression was above the level of the foramen magnum, only a small portion of the aneurysm extending below it. The part of the circumference of the cord or medulla subject to direct compression was in Case 1, right lateral; Case 2, right posterolateral; Case 3, right anterolateral; Case 4, anterior; Case 5, anterior; Case 6, right posterolateral; Case 7, left anterolateral.

Involvement of cranial nerves.—As was to be expected, owing to the level of the lesion, the 11th and 12th cranial nerves were severely affected in Case 6. The impairment of sensation in the trigeminal field was of a type and distribution which suggested involvement of its descending sensory root. In addition vertigo and nystagmus were

prominent. In Case 3, in which there was a considerable extension of the tumour above the foramen magnum, there were post-operative developments of interest. The involvement of the 11th cranial nerve was almost certainly due to traction upon it in the course of removal of the tumour (as also in Case 1). In this instance there was also evidence after operation of damage to the afferent trigeminal pathway, either the descending spinal tract or the nerve itself. The distribution of the sensory loss and abolition of corneal reflex suggest the latter.

Apart from Case 6, however, signs of cranial nerve involvement before operation were little in evidence. In Cases 2, 3 and 5 there were none. In Case 1 the tongue was protruded slightly to the right. In Case 4 on a single occasion a fine nystagmus was observed, as also in Case 7.

Elsberg [2], apropos of tumours between the 1st and 3rd cervical segments, states that cranial nerve symptoms are surprisingly infrequent, and signs referable to cerebellar disturbance very unusual. He mentions nystagmus, trigeminal hypæsthesia and facial weakness as occasional findings.

Abrahamson and Grossman [1], in five cases of compression at the level of the foramen magnum, observed nystagmus in two, but no other affection of the cranial nerves.

Rhein [9], in a report of a single case, records weakness of the right soft palate associated with dysphagia and dysphonia in an endothelioma filling the foramen magnum.

In Frazier and Spiller's case [5], of an endothelioma whose major bulk was above the foramen magnum and on the left side, there was atrophy of the left trapezius, and a marked fibrillary tremor with wasting of both sides of the tongue.

Globus and Strauss [7] make no mention of cranial nerve palsies in a case of endothelioma at the first cervical level with a small protrusion through the foramen magnum.

Kraus and Silverman [8] record unilateral lower facial paresis as occurring in seven out of ten cases of tumour at the high cervical level. Of these seven, five were extramedullary and two intramedullary.

Elsberg and Strauss [4] observed slight nystagmus to the left in a case of endothelioma, of which about one-third projected upwards through the foramen magnum.

It appears on the whole that, in the group of cases which form the object of this study, a tumour which does not extend above the foramen magnum is unlikely to cause any symptoms referable to the cranial

nerves, and that a tumour which straddles the edge of the foramen magnum is likely to cause symptoms of spinal cord compression of a kind and degree which overshadow any cranial nerve symptoms that may be present. If such symptoms are much in evidence before operation a large part of the tumour is probably above the foramen magnum.

The cervical sympathetic.—Some evidence of cervical sympathetic palsy was present in four of our cases (1, 3, 4 and 7). It appears to have been present in two of the six cases reported by Elsberg and Strauss [4] in which a tumour projected from spinal canal into foramen magnum. Cervical sympathetic palsy, therefore, seems to be an inconstant phenomenon in the syndrome under consideration.

Motor system.—In all seven cases spastic weakness of the limbs was prominent among the symptoms. In cases 1, 2, 3, and 6, in which the compression was to one side of the mid-line, the weakness was first noticed in the ipsilateral upper limb, then in the lower limb of the same side. In cases 2 and 3 the weakness subsequently progressed to involve the contralateral lower limb. So far as our experience goes, therefore, it confirms on the whole the observation of Elsberg already quoted, that in high cervical tumours the involvement of the limbs follows an order in which the ipsilateral upper limb is involved first and the contralateral upper limb last. Case 7 was exceptional in that no signs of pyramidal disease appeared till after lumbar puncture. The weakness when it did appear was confined to the upper limbs and affected both equally though the tumour was laterally placed.

Localized muscular wasting was present in five of our cases. In Cases 5 and 7 it was absent. In Case 4 there was generalized muscular wasting of both upper limbs. This was the case in which the compression was anterior. In the other four cases the compression was anterolateral, lateral or posterolateral, and in each, at one time or another, wasting of the intrinsic muscles of the ipsilateral hand was a striking feature. In Cases 2 and 3 it developed after operation, and in Case 3 was of sufficient degree and duration to be attended for a while by a *main en griffe* deformity.

Many observers in the past have commented upon the occasional occurrence of atrophy in the hand as the result of a lesion at a higher level in the cervical cord than would be considered appropriate in the light of accepted anatomical fact. Garcin *et al.* [6] report a case in which an endothelioma at the 5th cervical level gave rise to pronounced atrophy in both hands as well as in the shoulder girdles, so that the diagnosis of amyotrophic lateral sclerosis was first suggested.

Elsberg and Strauss [4] state that "atrophy of the muscles of one or both fore-arms and of the intrinsic muscles of the hands is frequent, not only in tumours which involve the lower half of the cervical cord but in those above the 4th cervical segment." We have no explanation to offer for this phenomenon. It may be due to a descending arterial supply to the motor cells concerned, which is liable to interruption as the result of compression at the level of the foramen magnum. As a fact of clinical observation the point is clearly of great importance, for misinterpretation may easily lead to a diagnosis of syringomyelia.

Paralysis of the diaphragm from a lesion at the first cervical level is also somewhat unexpected. Yet it occurred without doubt in Case 6 in association with an earlier story of hiccough. Frazier and Spiller's case [5] provides a comparable example—an endothelioma astride the edge of the foramen magnum, and indenting the left lateral aspect of the cord at this level, with paralysis of the left half of the diaphragm in addition to other symptoms and signs.

Sensation.—Of the *subjective complaints*, pain referred to the second cervical distribution on one or both sides, especially if, as in Case 1, followed by numbness, is a symptom to be expected when the lateral or posterolateral aspect of the cord is directly compressed. The importance of this symptom as a diagnostic point has been stressed by Elsberg and Strauss [4]. When present, it frequently precedes all other symptoms by a considerable interval. Cases 1 and 7 provide striking examples.

The sensation as of a tight band or collar around the upper part of the neck was a prominent symptom in Case 7, preceding the appearance of abnormal physical signs.

In the four laterally situated tumours of our series, pain, tingling or numbness referred to the ipsilateral arm, fore-arm and hand, was an early symptom in all. Comparable symptoms were also referred to one upper limb in Cases 4 and 5 in which the compression was anterior.

In Case 1 the numbness was confined to the thumb, middle and ring fingers of the right hand; in Cases 2 and 6 pain and tingling was more vaguely referred to the whole right arm and hand. The initial symptom in Case 3 is of extreme interest in its physiological aspect, the patient experiencing momentary paræsthesiæ in the right upper limb under a particular kind of emotional stress. Somewhat akin is the hyperalgesia or over-reaction experienced in the ipsilateral limbs in Case 1. The fact of great clinical importance is that in each of our seven cases subjective pain or paræsthesia was an early symptom, that in each case this symptom

first appeared in one upper limb, and that the upper limb involved was that first affected by spastic weakness.

This association of sensory with upper neuron motor symptoms in the same upper limb in the early story of high cervical tumours has been the subject of comment by previous writers (Elsberg [2], Elsberg and Strauss [4], Frazier and Spiller [5]). It is not easily explained. The sensory symptoms clearly cannot be attributed to pressure by the tumour upon appropriate roots, but must be due to interference with some intramedullary pathway. It is easier to assume that this pathway is the posterior column than to offer any alternative explanation consistent with the accepted tenets of anatomy and physiology.

The practical importance of this combination of symptoms lies in the fact that the story of progressive numbness and weakness of hemiplegic distribution may easily suggest the diagnosis of cerebral rather than spinal tumour. This diagnosis had indeed been considered in Case 1.

The next development in the sequence of subjective sensory symptoms in each of our five cases with lateral compression was that of paræsthesiæ in the contralateral upper limb. The distribution and character of these paræsthesiæ as they first appeared were thus described :—

Case 1.—This patient, a medical woman, spoke of "coldness along the ulnar border of the left hand and arm."

Case 2.—The patient was a Jewess with little English at her command, and described only tingling in the left hand.

Case 3.—"Numbness in the left little finger gradually spreading across the hand to include the other fingers and thumb."

Case 6.—"Numbness of the little and ring fingers" spreading up the inner border of the forearm to the elbow.

Case 7.—"Numbness in the right hand."

The correspondence of distribution in three of these five cases is so close that it must surely be related to the position of the lesion. In each instance the right lateral aspect of the cord was compressed at the level of the foramen magnum. The observation suggests that at this level there is some anatomical arrangement of the fibres in the spino-thalamic pathway which results in those from the hand, and especially from the ulnar side of the hand, lying most superficially. Some such arrangement has been postulated by Tilney and Elsberg [12], but their diagrams would not explain our observations. They postulate a lamellation of the fibres so that those from the sacral segments lie most superficially and posteriorly. Pressure, therefore, upon the antero-lateral aspect of the cord might at first spare the lower, and pressure on

its posterolateral aspect, the upper segments. But in both Case 2 (posterolateral) and Case 3 (anterolateral) the early reference of paræsthesiæ to the lower rather than the upper cervical segments was associated with some degree of preservation of sensibility in the sacral segments.

The character and distribution of the *objective sensory loss* in our cases corresponds on the whole with what has been observed by others in compression of the cord at this level. Elsberg and Strauss [3, 4] in particular have emphasized the dissociated character of the cutaneous sensory defect. A severe degree of loss to painful and thermal stimuli may be associated with a normal response to tactile stimuli as judged by clinical standards. Furthermore, there may be not only dissociation between the response to heat and cold, but between thermal and other kinds of pain.

These observations are confirmed in every point by our own observations. In relation to the persistent area of over-reaction to cold in the thoracic region in Case 3, we are impelled to quote Elsberg [2 verbatim: "... in many cases the patient is unable to recognize hot at a time when he is still able to recognize extreme cold. ... In some instances hot is not recognized at all, but cold, though not recognized as such, is distinctly painful. ... It is a very interesting fact that this perversion of cold in which cold is not recognized as such, but is felt as pain, may be found over areas in which pain as tested with a sharp needle, and even pain due to deep pressure, has been entirely abolished." Practically the recognition of the occurrence of such dissociated anæsthesia in high cervical tumours is of importance in the differential diagnosis from syringomyelia.

In each of the five cases in which the tumour was laterally placed there was some sensory defect *on the same side as the lesion.* In four of these cases the defect was confined to the area of the upper cervical segments (Cases 1, 3, 6 and 7). In Case 2 it was much more extensive. The distribution of the *contralateral* cutaneous sensory defect in Case 1 covered all segmental areas up to and including the second cervical, but with an ill-defined upper level. The distribution in Case 2 was similar, but with relative sparing of the sacral segments. Again, the upper level of sensory defect was indefinite. In Case 3, in which the tumour was anterolateral, the upper level was sharply defined, and corresponded exactly with the boundary between the trigeminal and second cervical fields. In this case the relative sparing of the lower thoracic segments for pain and cold was a striking feature, and there was also sparing of

the sacral segments for heat only. In Case 6 the maximal defect was confined to strips of roughly segmental distribution in the upper and lower limbs, with less involvement of the rest of the limbs and upper trunk, and escape of the lower trunk.

In Case 7 the contralateral as well as the ipsilateral defect was confined to the upper three cervical segments.

In Case 4, in which the compression was anterior, at the first examination the sensory defect was confined to the medial border of right upper limb and right trunk, and in Case 5, again with anterior compression, there was impairment over the 2nd to 4th cervical segments on both sides, and below this, over the whole of the limbs and trunk on the right.

The simplest explanation of the bilateral defect in the upper cervical segments observed in several of these cases is that, at the level of compression there was impairment of conduction, not only in the spinothalamic fibres, but in those of the root entry zone on both sides.

The relative and absolute escape from sensory loss of large segmental areas on the trunk observed in Cases 3 and 6 respectively, aroused in each instance the suspicion that there might be two separate lesions of the spinal cord at different levels. This possibility was disproved at post-mortem in Case 6, and the post-operative course in Case 3 makes it highly improbable that there was a second lesion in this case. Such escape of intermediate segments depends presumably upon a lamellar arrangement of the fibres in the spinothalamic tracts, as has been suggested by Tilney and Elsberg [12], though it cannot be explained in terms of the pattern which they represent.

Sensory defect of the type which depends upon interference with the posterior columns was a conspicuous feature in six cases, but conspicuously absent in Case 1. In this case, the position of the tumour in relation to the transverse section of the spinal cord (lateral) differed very little from that which obtained in Cases 2, 3 and 7 (posterolateral and anterolateral), but in the latter cases the disturbance of posterior column function was severe; in these three cases, however, as also in the others of this series, the degree of compression of the cord as a whole, as judged by the clinical evidence, was considerably greater than in Case 1. In Cases 4 and 5, in which the cause of compression was anterior, there was extensive and severe loss of posterior column function, but this was at a stage when bilateral spastic weakness was advanced. Our conclusion, therefore, is that in compression at this level, the time of onset of posterior column involvement depends rather

upon the degree of compression of the spinal cord than upon the site of incidence of the compression in relation to the circumference of the cord. This view is in agreement with that of Elsberg [2] who states as a rule that disturbance in vibratory and articular sense in spinal tumours always occurs when the pressure has affected the entire thickness of the cord, whether the growth is ventrally or dorsally placed. Dissociation between defect in the sense of passive movement and that of vibration was evident in Cases 2 and 5, in which there was loss of vibration with preservation of postural sense, and to a lesser degree in Case 6, in which vibration sense was partly preserved, while postural sense was lost. Similar dissociation may be sometimes observed in cases of intramedullary disease, for instance, in tabes, subacute combined degeneration, and disseminated sclerosis. Its occurrence in compression of the cord by tumours has before been noted by Elsberg [2]. The distribution of the defect of posterior column sensibility in Cases 2, 3, 5 and 6 conformed to a type which we suggest may be a characteristic feature of compression of the cord at this level at certain stages in its development. In Case 2, vibration sense was lost over the whole right upper limb and clavicle, unimpaired elsewhere; postural sense was impaired in the right fingers. In Case 3, vibration sense was lost over the trunk and both upper limbs, including the clavicles and iliac crests, and in right lower limb, unimpaired in the left lower limb. Postural sense was lost in both hands, slightly impaired in the right lower limb, unimpaired in the left lower limb. In Case 5, vibration sense was lost over the right trunk and limbs up to and including the acromion process, and over the left lower limb, preserved over left trunk and upper limb. Postural sense was defective in the right thumb, elsewhere normal. In Case 6 vibration sense was impaired in the right upper limb up to and including the clavicle. Postural sense was lost in both upper limbs, unimpaired in the lower limbs. In Case 7 both postural sense and vibration sense were lost in both upper limbs (including loss of vibration sense over the clavicles), with partial loss in the fingers and relatively little defect in the lower limbs.

Thus in each of these cases the defect of posterior column sensibility, as measured by one or other test, was practically confined to one or both upper limbs. This distribution suggests that the fibres which enter the posterior columns from the posterior root entry zone at first lie superficially, and thus suffer first and more severely from the effects of compression. Evidence in favour of a strictly lamellar arrangement

of the fibres in this fashion is provided by the observations made in Case 3 during the stage of recovery, when the defect of postural sense was minimal in the fingers and wrist, greater at the elbow, and maximal at the shoulder, and vibration sense remained impaired over the acromion after it had returned to normal over the remainder of the upper limb.

It is worthy of note that in Cases 2 and 3 the post-operative return of posterior column function from severe impairment to normal took only a few weeks. It is probable that the development of this form of sensory loss during the progress of compression may be equally rapid. This was shown in Case 7 and appeared to be so in Case 4, in which, however, the patient's inadequate ability to co-operate over sensory tests impaired the value of the observations.

Reflexes.—The disturbances of reflex function need little comment. Massive reflex movements of the upper limbs of the type described by Buzzard and Riddoch [10] were observed in Cases 3 and 5 only.

Sphincter control.—In Case 5 only was there any disturbance of sphincter control. This is in opposition to the opinion expressed by Abrahamson and Grossman [1] that bladder and rectal disturbance occur early and are frequently the first symptoms in cases of high cervical tumour. Stookey [11], however, as the result of an analysis of a series of cases of spinal tumour with reference to this point, concluded that above the level of the conus there was no relation between the level of the lesion and the time of onset of sphincter disturbance.

Vertebral column.—Clinical examination revealed some abnormality of the cervical spine in each case, though in no instance was this striking. It was observed only when especially looked for. In the five cases of tumour, active or passive movement of the head upon the neck in one direction or another was associated with, and limited by pain. Tenderness on pressure over the upper cervical spines was present in Cases 1, 2, 4 and 5, but only severe in Case 4.

Cerebrospinal fluid.—In Cases 5 and 6, Queckenstedt's test was negative and the protein content in the fluid was within normal limits. It is to be noted that these were the two cases in the series in which the compression was not due to new growth.

The five cases of tumour all showed some abnormality. In Case 1 Queckenstedt's test was negative. In the other four cases, on jugular compression, either the rise, or the rise and fall of pressure were slower than the normal. In Case 1 the protein was slightly raised (80 mg. on the first and 60 mg. on the second occasion). In Cases 2, 3 and 4 it ranged from 100 mg. to 200 mg., whilst in Case 7 it was 1,200 mg.

These findings correspond with what may be observed in extramedullary tumours at other levels, except that the degree of subarachnoid block in relation to the severity of the clinical symptoms, would appear to be less in these cases of high cervical tumour than it is at lower levels. Of particular interest was the exceptionally high protein content in Case 7 with evidence only of partial block at a stage when no abnormal physical signs had not yet been discovered.

X-ray examination.—No abnormality of the cervical spine was seen in any case. A cisternal puncture for the purpose of lipiodol injection was attempted and failed in Cases 1 and 2. It is probably a dangerous procedure in compression at this level, and unlikely to give successful results. Injection of lipiodol by lumbar puncture, and examination on the tilting table, head downwards, appeared to be the method most likely to provide visual evidence of the lesion. It was used in four cases with variable, and, on the whole, disappointing results.

In Case 1 only was the lower border of the tumour accurately defined. In Case 3 there was no adequate movement of the lipiodol, although the patient was tilted head downwards for several minutes. In this case, the degree of subarachnoid block was considerable, and the residual pressure after withdrawal of cerebrospinal fluid was 5 mm. It seems possible that the lipiodol injected forty hours later found the subarachnoid space empty and collapsed, and was unable with the aid of gravity to force a passage. After the event, we considered that we should have injected enough saline to fill the subarachnoid space before introducing the lipiodol.

In Cases 2 and 5 the results of this examination were misleading. The flow of lipiodol was arrested at the level of the 6th and 5th cervical vertebræ respectively. In each instance the movement of the lipiodol as viewed with the screen was steadily maintained up to the level of arrest.

All the observations were made through the generosity and with the help of Dr. H. M. Worth, and the same technique used in each case. We have no explanation to offer for the discrepancies, but conclude that in the reversed position of the body, arrest in the upper cervical region, unless it shows the convex outline of a tumour, is not to be relied upon as a guide to localization.

The early symptoms in cases of tumour.—The five cases of tumour (four endotheliomas and one neurofibroma) form a group of more or less uniform pathology, all being fibrous growths of slow development. In all save one pain at the back of the head and neck was the earliest symptom. The exception was Case 4, in which the tumour lay

on the anterior surface of the cord; here paræsthesiæ and weakness in one upper limb were the earliest symptoms, and a vice-like pain at the back of the head appeared only as a late symptom.

In the other cases, suboccipital pain was the leading or only complaint for months or years before other symptoms developed. In Cases 1 and 7 it continued as the only symptom for five and three years respectively. In Case 2 it preceded other symptoms for about one year. In Case 3 it was the leading symptom for about one year, being associated with occasional paræthesiæ in one arm.

After the suboccipital pain, paræthesiæ in one or other hand was the next symptom to appear in all five cases. In Case 7 these symptoms were followed by the band-like sensation around the neck. In this case the rapid development of physical signs following lumbar puncture was of particular interest. After a period of nearly four years, during which the symptoms were entirely subjective, the signs of compression were fully developed within three days of the removal of 4 c.c. of cerebrospinal fluid.

Note on the Surgical Approach (Julian Taylor).

To expose the foramen magnum it is best to have the patient lying belly downwards with the neck flexed. Flexion of the neck may embarrass respiration where there is foraminal block, and thus the degree of permissible flexion must be determined in consultation with the anæsthetist before the operation is begun, but the technical advantage afforded is so great that the flexed position cannot altogether be abandoned on account of possible danger. The scalp and neck are incised in the middle line from the external occipital protuberance downwards and the first three cervical arches are removed. The dura is inspected and the presence or absence of respiratory pulsation is noted. If it be clearly seen in the suboccipital region it is certain that a tumour, if present, is well below the foramen, especially where cerebrospinal fluid block has been previously demonstrated. Respiratory pulsation of the normal theca in this region is of such amplitude that its observation leaves little opportunity for error, either in recognition or in consequent deductions regarding the level of a possible tumour. If a tumour blocking the foramen be thought to be present, part of the occipital bone is then removed, a fairly extensive craniectomy being advisable. The dura of the posterior fossa and the spinal theca are then opened above and below the foraminal constriction and the incisions are joined. The advantage accruing from the large craniec-

tomy is then seen if, as the result of tumour growth in the foramen, the normal venous sinuses of the dura be found greatly increased in capacity and number. On opening the dura and exposure of the arachnoid the earlier observation regarding pulsation is checked. With inspiration and expiration the ebb and flow of fluid through the unobstructed foramen is so freely tidal that there is now no possibility of erroneous deduction, but if pulsation be absent something is unquestionably blocking the foramen, and thus if no tumour be seen there must nevertheless be one situated either in the central nervous substance or anteriorly. A cerebellar tumour is at once obvious, but at this stage, unless there is evident lateral displacement of the medulla, it may be difficult to distinguish between a medullary tumour and one anteriorly placed. An anteriorly or anterolaterally placed growth almost necessarily entails division of the first and perhaps the second posterior cervical roots, a step that usually permits the operator to rotate the medulla far enough to gain a view of what lies in front. It will usually afford enough room to enable him to remove a tumour, but the anterior roots and the accessory nerve may sometimes be in the way. The decision to divide even posterior roots may be a difficult one to make in the case of a patient whose diaphragm and intercostal muscles are paralysed and whose breathing is precariously dependent on the intact accessory and second cervical nerves.

When a neurofibroma has been found it is obviously necessary to remove a part of the affected nerve root, and when an endothelioma is present there are usually adhesions to the surrounding nerves, dissection of the tumour from which must be carried out with the precision that the situation demands. The removal of an endothelioma may at first appear to present formidable difficulties, but a successful attempt to free the tumour from its dural attachment may render it unexpectedly docile, when removal may be effected without difficulty. It is obvious that the force of manipulations in this region is transmitted undiminished to the medulla, and thus that sudden fluctuations in the pulse frequency, blood-pressure and respiration may be experienced. If the operator therefore finds this part of his task anything but effortless, or if his attempted division of a dural attachment has failed, he must then proceed to remove pieces from the accessible part of the tumour, in order that the remaining deeper part may be more easily displaced. For this purpose the writer's preference is the use of the knife to that of the diathermic cautery owing to the proximity of the vital medullary centres. These endotheliomas have not been highly vascularized and

there has been little bleeding on incising the tumours. The bared dura may, however, bleed freely from opened veins, but the hæmorrhage is easily stopped by a temporary application of muscle grafts. The occipital bone is sometimes invaded by the growth, in which case the operator must decide for himself whether in a life-saving operation of this sort he should undertake the technically difficult, but pathologically correct, procedure of removing affected bone from the anterior or lateral part of the foraminal edge. The bone here normally encloses venous lakes and these may well be increased by endotheliomatous invasion. The tumour gone, there appears at once the respiratory ebb and flow of fluid from the posterior fossa, and even if the respiration and pulse have been seriously affected by the manipulations there soon returns a good pulse and regular breathing of satisfactory depth. The wound is then closed in the ordinary way by suture of the muscles and skin. As in other procedures in the posterior fossa the operator must be prepared for reactionary depression of the respiratory and cardiovascular functions during the hours following the operation.

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MULTIPLE MENINGEAL AND PERINEURAL TUMOURS WITH ANALOGOUS CHANGES IN THE GLIA AND EPENDYMA (NEUROFIBROBLASTOMATOSIS).

With Report of Two Cases.

BY C. WORSTER-DROUGHT, W. E. CARNEGIE DICKSON, AND W. H. McMENEMEY.

(From the West End Hospital for Diseases of the Nervous System, London).

Introduction.

In the *Edinburgh Medical and Surgical Journal* for 1822 there appeared an article by J. H. Wishart, entitled "A Case of Tumours in the Skull, Dura Mater and Brain." His patient was a youth, aged 21, who complained of bilateral deafness of recent onset and of a small tumour on the back of his head. Two years later he was absolutely deaf and blind, the pupil of the left eye being "completely dilated as in a case of amaurosis." The patient had been blind in the right eye since soon after birth. The tumour on the back of his head had grown considerably and it now caused him a great deal of pain. He experienced "very peculiar and disagreeable smells," severe frontal headaches and attacks of vomiting, and died soon afterwards. The autopsy was performed by Wishart, who found numerous tumours attached to the dura mater, most of them arising from the falciform process. A tumour about the size of a split pea and of considerable hardness was attached to the left 5th cranial nerve, while on that of the right side were several small nodules. There was a tumour attached to each "7th nerve" (in all probability the 8th nerve is meant) just at the entrance to the internal auditory meatus. Multiple tumours were found upon the nerve-roots throughout the whole extent of the "medulla spinalis." Wishart concluded that "it is most probable that these tumours on the nerves arose rather from the dura which envelopes them than from the nervous substance itself."

Similar cases have been recorded from time to time, but Wishart's appears to be the first to be published. In a review of the literature of multiple meningeal tumours, Hosoi (1930) collected ten examples of this particular type, including one of his own. Three other cases occur in

the literature prior to 1930, those of Soyka (1877—first case), Kaulbach (1906) quoted by Stewart and Copeland, and of Christin and Naville (1920). Since the publication of Hosoi's paper, further examples have been recorded by Kernohan and Parker (1932), Katzenstein (1932), Cabot and Smith (1933) and by Shapland and Greenfield (1935).

This syndrome of multiple meningeal tumours associated with neurofibromata (of which there are apparently seventeen cases on record) is but one variety of the not uncommon disease of the central nervous system "central neurofibromatosis," or "central von Recklinghausen's disease." The former term has been in common use since 1900, but apparently it was not employed by von Recklinghausen himself.

Papers by numerous authors have dealt with the ætiological, clinical and pathological aspects of "neurofibromatosis," but there is still some lack of agreement as to the correlation and exact nature of the pathological lesions. It is the purpose of the present communication to record details of two further examples of the relatively rare syndrome originally described by Wishart and to suggest a clinical and pathological classification of "neurofibromatosis."

Case 1.—C. K., male, a house painter, aged 25, was admitted to the West End Hospital for Diseases of the Nervous System, London, on September 12, 1932, complaining of "dizziness, headache and noises in the ears." The total duration of illness prior to admission was eight years.

Eight years previously (1924) appendicectomy was performed in another hospital, the appendix being retrocæcal and containing pus. According to the notes he looked pale and ill and had conjunctivitis (whether unilateral or bilateral not stated). A month or two later he noticed the right eye bulging and a discharge from the right nostril. He returned to hospital with proptosis of the right eye, the movements of the eyeball being of full range. "Nasal polypi" were found on several occasions and removed. A note at this time states that congenital cataract was present in both lenses.

Two years later (1926) he was readmitted to hospital on account of a return of the right-sided nasal obstruction and discharge. Operation was performed for what was described as a right ethmoid "mucocœle" and a right-sided "nasal polypus." The right frontal sinus was intubated. The right eye was proptosed, but both pupils reacted to light and on accommodation. After the intubation there was no noticeable change in the condition of the right eye.

A year later (1927) he was unable to extend fully the middle finger of his left hand. Within a fortnight the weakness had spread to involve the extensors of all the fingers of the left hand. After a month or two wasting and gradually increasing weakness of the whole of the left leg developed.

Three years later (1930) he was again admitted to hospital in a condition very similar to his present state (1932) with the exception that he had, at

that time, no defect of speech. A biopsy was performed on a small tender nodule found on the back, the report stating that it was a "typical neurofibroma."

Six months later (1931) he began to lose sight in the right eye, and a few months later became deaf on the left side. Early in 1932 he complained of headache for the first time, frontal in situation, severe and continuous, and aggravated by movement.

In June, 1932, he was admitted to the Metropolitan Hospital under the care of one of us (C. W.-D.). Here a biopsy was performed on a small portion of tumour removed from right orbit. The report stated that it was an "endothelioma showing psammoma-like bodies."

The patient was later transferred to the West End Hospital for Diseases of the Nervous System.

Past history.—He had never been robust. Between 1925 and 1928 (i.e. seven years before admission to this hospital) he had had four attacks of pleurisy, but paracentesis thoracis had never been performed. There was no history of fits. He was moderate in the use of alcohol and tobacco.

Family history.—He was one of a family of eleven, of whom seven and also both parents were still alive and well. There was no family history of mental disease, epilepsy, deafness, paralysis, skin-tumour or moles.

Condition on examination (*September*, 1932).—The patient was a poorly nourished pale young man of slender build with no clinical indication of endocrine dysfunction. There was a marked degree of proptosis of the right eye, which was totally blind. Its movements were restricted in all directions. The pupil was circular, central, regular, and of normal size, but its reactions to light and on accommodation were sluggish. The fundus could not be seen on account of an intraocular opacity.

The visual acuity of the left eye was poor, but he could recognize fingers at one foot. The pupil was central, regular and of normal size; its reactions to light and on accommodation were sluggish. The ocular movements were of full range, with fine nystagmus in all directions. The fundus showed some four dioptres of papillœdema, but accurate measurement was difficult owing to a semicataractous lens. No retinal tumours were identified. During sleep the left eye remained partially open.

The left corneal reflex was diminished, but the motor functions of the 5th cranial nerves were intact. A left-sided facial paralysis of the infranuclear type with slight muscular wasting was present. There was complete nerve deafness on the left side and partial on the right. The right side of the tongue was weak but not wasted. Speech was loud and somewhat explosive. The functions of the other cranial nerves were not impaired.

Upper extremities: There was left-sided wrist drop with wasting of the extensor group of muscles of the forearm. The supinator jerk was absent on this side but present on the right. The biceps and triceps jerks were present on both sides, but brisker on the right.

Lower extremities: The calves and thighs on both sides were wasted, more

so on the left. Fibrillary tremors were observed in the wasting muscles. Bilateral pes cavus was present. The right knee-jerk was exaggerated, the left absent. Both ankle-jerks were absent. The right plantar response was flexor, the left extensor. The abdominal reflexes were present on the right, but absent on the left side.

Sensation: Owing to the patient's deafness observations were difficult. There appeared, however, to be a diminution in sensation to pinprick over the areas supplied by both 5th cranial nerves, and diminution of pain sensation over the left forearm on distribution of the 8th cervical root. Vibration and deep pain were appreciated in both lower extremities. The contour of the spine was normal and all its movements full.

The patient's gait was very ataxic, but there were no tremors at rest. The bladder was not distended; micturition and condition of the urine were normal.

No swellings were palpable on any of the peripheral nerves and there were no cutaneous manifestations of neurofibromatosis, apart from the nodule removed from the back for biopsy at an earlier stage, or of tuberous sclerosis, i.e. he had neither *café au lait* patches, vitiligo nor nævi, either vascular or pigmented, nor adenoma sebaceum. There were no palpable irregularities in the contour of the skull or of the long bones.

The chest was poorly covered and expansion diminished. No abnormality was detected in the heart or lungs; the average pulse-rate was 100. The blood-pressure varied between 105/70 and 90/60. No abnormality was detected in the abdomen. The liver, spleen and kidneys were not palpable.

He appeared of average intelligence and his behaviour in the ward was in every way normal. He co-operated as well as his deafness would allow and was quiet and composed, exhibiting no evidence of euphoria.

Investigations.—The cerebrospinal fluid, eight weeks before death (Dr. H. C. Lucey) was yellowish and under considerable pressure. No clot formed on standing. Four small lymphocytes were present per c.mm. Total protein was 0·1 per cent. The Wassermann reaction was negative in both the fluid and blood.

Electrical reactions (Dr. Sainsbury): Faradic responses were easily obtained in all muscles of the left arm except in the extensor communis digitorum and extensor longus pollicis. In these latter muscles complete reaction of degeneration (R.D.) was present and no galvanic reactions were obtained. In the lower extremity all responses were easily elicited except in the tibialis anticus and the intrinsic muscles which showed absolute R.D. Faradic responses were obtained on the left side of the face and the galvanic reactions were fairly brisk.

Progress of case.—Repetition of lumbar puncture was not considered justifiable as the patient's condition had rapidly become worse. Headache was considerable, partial relief being obtained with intravenous hypertonic saline. He died on October 29, 1932, after twenty-four hours' coma. Throughout his stay in the Metropolitan and West End Hospitals he remained apyrexial and had no fits.

AUTOPSY.

The body was that of a fairly tall emaciated young adult male, with no appreciable difference in the size of the two lower limbs, but with more marked atrophy of the extensors of the left than of the right forearm. No nævi or patches of pigmentation in the skin and no subcutaneous nodules were found. There still remained a moderate degree of proptosis of the right eye, the pupil of which was distinctly larger than that of the left.

Cranium: No subcutaneous nodules were found in the scalp. The skull-cap was of moderate thickness, somewhat irregular and distinctly asymmetrical, with only scanty diploë, and with no periosteal swellings or any of the hyperostoses sometimes found in the bone over subjacent meningiomata.

FIG. 1.—*Case* I. Inferior aspect of brain to show the meningiomatous tumour involving the right olfactory bulb. The underlying dura was infiltrated by it. On either side of the much compressed pons lie the cerebello-pontine angle tumours and, external to each of these, is a portion of the temporal bone containing the internal auditory meatus.

The dura mater was easily separated from the interior of the skull, and, scattered over its arachnoid surface, were some fifty small projecting tumours varying up to half a pea or a small bean in size, most of them firm and slightly nodulated, others somewhat friable and "cauliflower-like." The three largest, approximately equal in size and some 8 by 10 mm., projected into and indented, but were not adherent to, the surface of the hemispheres. These tumours did not show any outward infiltration nor had they caused any

erosion or indentation of the bones of the skull. There were four small plaques of similar growth projecting slightly from the surface of the falx cerebri and several on the under surface of the tentorium cerebelli. A number of smaller tumour-like masses of like nature projected into the lumen of the superior sagittal sinus. Both middle ear cavities appeared healthy and were not invaded by tumour.

The brain weighed 1,450 grm. Its surface was slightly flattened and congested with a certain amount of external hydrocephalus and a small pressure-cone at the base. The olfactory bulbs were embedded in a friable gritty mass growing from and invading the meninges over the cribriform plate, through which it had passed into the upper part of the nasal cavity (fig. 1). It also extended into the right orbit and surrounded the optic nerve as far as the back of the eyeball, which itself was not invaded. At each cerebello-pontine angle there was a large irregular nodular tumour, firm in consistency and attached to the 8th nerve. That on the right side measured 24 by 23 by 22 mm., and on the left 40 by 36 by 33 mm. The left tumour had invaded the temporal bone. The lower half of the pons on each side and the anterior aspects of each cerebellar hemisphere were deeply compressed and indented. On each 3rd nerve was a tumour, that on the right measuring 3 mm. and on the left 5 mm. in diameter. On the left 5th nerve there were several small tumours up to 4 mm. in diameter: another 1½ mm. on the right 6th nerve; while the left 6th nerve did not show any visible swellings but was compressed by the acoustic nerve tumour, as was also the right 6th nerve. A string of small tumours up to the size of hempseeds was situated on the left 9th, 10th and 11th cranial nerves; and there was a similar but smaller series on the corresponding nerves of the right side.

On horizontal section through the cerebral hemispheres, several small patches with an unusual fine fenestrated appearance were found, mostly in the subcortical white matter, particularly in the right inferior frontal gyrus and in both superior parietal lobules. Other whitish and slightly depressed patches in the gray matter involved the surface and had a slightly firmer consistence than the neighbouring cortex. Over these the leptomeninges were appreciably thickened and adherent. The ventricles were slightly dilated, but without any ependymal "granulations" or nodules, and to the naked eye the choroid plexuses appeared normal. Apart from compression by the acoustic nerve tumours, there was no obvious abnormality of the cerebellum. The pituitary was of normal size.

Spinal Cord and Nerve-Roots: Numerous small irregular tumours, several hundred in number and varying in size from minute swellings just visible to the naked eye to slightly larger than a hemp-seed, were found upon the nerve-roots, particularly upon those of the cauda equina; sometimes a dozen or more were present upon a single root, and reminiscent of Alexis Thompson's description: "grains of boiled tapioca on a string." In addition to these, there was a larger nodulated mass, not unlike a miniature corncob in appearance, 33 mm. in length by 11 mm. in diameter, lying upon a nerve-root within

the membranes posteriorly and somewhat towards the right at the level of the termination of the cord. This mass was loose and practically unattached save for a thin elastic thread suggestive of a blood-vessel rather than a nerve but at its lower end a definite nerve-root emerged. No tumours were visible on the filum terminale. In the upper cervical region, at the level of the lower margin of the atlas, there was an irregular, rather tufted or slightly cauliflower-like mass of growth, adherent to the inner surface of the dura, which, on microscopical examination, was a meningioma.

Most of the tumours were situated on posterior nerve-roots. The cord itself was here and there considerably distorted from compression by these tumours, and also by other tumours arising from the meninges. A certain amount of irregular cavity-formation was also present, particularly in the cervical region. Several of the spinal nerves were traced through the intervertebral foramina, but no naked-eye tumours were found upon them nor upon the intercostal nerves. No nodular masses were found upon the cervical, brachial, lumbar or sacral plexuses, nor upon the sciatic nerves and their branches, even when traced as far as the muscles of the calf.

Other Organs: Except for some fatty infiltration of the heart, nothing noteworthy was found in the viscera. No naked eye evidence of tumour formation was present in the suprarenals, in the sympathetic trunks or in any of the sympathetic plexuses. The thymus was persistent and moderately large, weighing 18 grm. The thyroid appeared normal.

Histology.

Meningeal tumours (intracranial).—Sections through the nodules projecting from the inner surface of the dura over the cerebral hemispheres showed a moderately cellular growth with the cells and their processes arranged in definite whorl formation, but also with some palisading. In the centre of many of the whorls a small vessel in some stage of hyaline degeneration could be identified. In the more gritty and friable tumours, calcification and the formation of "brain-sand" particles had also occurred. The friable spongy mass of tumour infiltrating the meninges and bone of the olfactory grooves and neighbouring structures was of this nature, and component psammomatous bodies in grape-like clusters could be demonstrated in teased toluidin blue preparations, the stalks being represented by branching blood-vessels. Sections of several of the smaller dural nodules resembled those of the cerebello-pontine angle tumours and, except for the presence of varying numbers of concentric psammoma-bodies, many of them were indistinguishable from these. Small psammomatous tumours, larger and more cellular than the adjacent Pacchionian bodies, projected through the walls of the superior sagittal sinus into its lumen.

Cerebello-pontine-angle tumours.—Sections of these showed on the whole a "whorled" rather than a "palisaded" arrangement of the fibres, giving an appearance intermediate between the typical neurofibroma ("perineurial fibroblastoma" of Penfield), and the typical meningioma ("meningeal fibro-

blastoma " of Penfield). In some areas, however, " palisading " was definitely present. Parts of the tumours showed considerable reticulation with almost complete disappearance of the cells. As is often found in acoustic nerve tumours when stained by van Gieson's method, the component fibres showed a " terra-cotta " tint, rather than the usual pink colouration typical of collaginous fibres. In the more " palisaded " areas, and in those parts where the growth was evidently more active, the nuclei were plump and oval in shape, vesicular, and with a distinct nuclear membrane, the chromatin being scattered in small particles throughout. In those parts of the tumours where the fibres were thin and fully formed, the nuclei were narrower, more elongated and stained more deeply and diffusely. These tumours were comparatively non-vascular with only a few thin-walled capillaries, many of them resembling blood-sinuses. With silver impregnation and with Mallory's connective tissue-stain, the reticulin was found to be confined to the adventitia and immediate neighbourhood of the vessels. In Bielschowsky da Fano preparations no nerve-fibrils were detected.

Cerebral cortex : " meningio-angiomatosis."—For the investigation of this process sections selected from one of the patches in the posterior part of the right middle frontal convolution were stained by the Weigert-Pal method ; these showed what might be described as a meningio-angiomatous condition of the cortex and a curious fenestrated appearance of the subjacent white matter, due to its spread into the latter (figs. 2 and 3). The blood-vessels of the lepto-meninges had very much thickened walls, and were in striking contrast to the sinus-like thin-walled blood-spaces seen in the acoustic and meningeal tumours. These pial vessels showed active proliferation and penetrated into the gray matter along with surface meningiomatous cells (*not* connected with the meningiomata described above). The process was thus a mixed lepto-meningiomatous and angiomatous condition of some chronicity (fig. 3). In this connection it is of interest to recall the syndrome described by Kalischer (1901), Parkes Weber (1929), and more recently by Bergstrand (1935), who regards it as comparable with central neurofibromatosis and Lindau's disease as well as with tuberous sclerosis. Lindau (1930) himself refers to certain gliomatous brain tumours characterized by abundant vascular proliferation, for which he suggests the descriptive term " nævi glio-vasculosi." The glial cells of the invaded areas also took part in the proliferative process, some of them being multinucleated and reminiscent of the " Gemästetezellen " found in tuberous sclerosis (fig. 4). The glial meshwork is much increased and the fibrils are coarse and thick. There also appears to be some patchy proliferation of oligodendroglia, and, throughout many of these areas of meningio-angiomatosis and gliomatosis, comparatively numerous surviving cortical nerve-cells are to be seen surrounded by these proliferative changes.

Choroid plexus.—Sections of the plexuses of the lateral ventricles showed in some parts considerable degenerative thickening of the cores of the villi but survival of the surface choroid epithelial cells ; in other portions there was hyaline swelling of the connective tissue around the central capillaries and

degeneration and disappearance of the surface cells. In Perdrau-stained preparations, concentric "brain-sand particles" were well seen, and were of much larger size than, but otherwise indistinguishable from, those of the meningeal tumours.

Ependyma.—The surface ependymal cells were absent over considerable areas but, where present, they were comparatively normal in appearance, although in places they were flattened and degenerated, with occasional small patches of subependymal gliosis containing little groups of ectopic ependymal cells, suggestive of the similar phenomenon often found in the neighbourhood of the central canal of the spinal cord. Small amyloid bodies were also distributed irregularly in considerable numbers throughout the subependymal tissues.

Spinal cord: root neurofibromata.—Sections through some of the lumbar posterior nerve-roots showed all stages in the development of the tumours from single small concentric whorls growing in and from any part of the sheath of the roots, up to the large naked eye tumours already noted. Sections stained by Perdrau's method demonstrated clearly the concentric fibrils of reticulin. The general appearance was suggestive more of a non-psammomatous meningioma than of a neurofibroma, but some of the tumours showed appearances intermediate between these two types of neoplasm. A noticeable feature was that, as these tumours gradually enlarged, the surviving nerve-fibrils tended to become expanded into a thin irregular capsule around them. It is interesting that this feature was noted in a solitary nerve tumour by Cheseldon in 1740. Transverse sections through, for example, a lumbar root showed the initial stages in the formation of the tumours (fig. 5), even the smallest having a distinctly concentric whorled structure and appearing to arise from the connective tissue sheath of the nerve-bundle. These tumours when stained by Perdrau's method were seen to have a very varying content of reticulin fibrils; in some there was a considerable amount, in others practically none.

Spinal cord: intramedullary neurofibromata.—These tumours were very similar to the above, being intermediate in type between typical meningiomata and typical neurofibromata. In the same microscopical section, and even in the same field, were seen tumours, in some parts whorled as in a meningioma and in others palisaded as in a neurofibroma.

Spinal cord: intramedullary astrocytomata.—The cervical enlargement contained an intramedullary tumour consisting of finely fibrillated spindle-shaped glial cells—a "fibrillary astrocytoma" which appeared to have developed from the grey matter; it was not an ependymoma derived from central ependymal cells, proliferating groups of which were also present in its neighbourhood.

Spinal cord: ependymal reactions and syringomyelic cavitations.—Transverse sections of the spinal cord at various levels showed a process resembling syringomyelia, most advanced in the lumbar region (fig. 6) with a considerable area of gliosis surrounding the central cavity. In the cervical

and dorsal segments there was as yet no cavity-formation, but small tumour-like proliferations of ectopic ependymal cells were numerous. There was marked distortion of the cord, and degenerative changes had occurred in much of the white matter. In places a commencing proliferation of the central ependymal cells and a pericentral gliosis were visible.

Sympathetic ganglia.—Sections through a ganglion in the neighbourhood of the left suprarenal gland showed several small scattered areas of proliferation of the stroma indistinguishable from the neurofibromatous process found elsewhere in this case.

Sciatic nerve.—A transverse section through the trunk of the left sciatic nerve revealed the formation of a few minute concentrically arranged nodules similar to those found in many of the spinal nerve-roots (fig. 7). In structure they are rather reminiscent of a Pacinian touch corpuscle.[1]

The pituitary body was congested and showed some predominance of the eosinophil cells, with distinct intermingling of the pars anterior with the pars posterior, the glandular cells of the former "overflowing" into the anterior part of the latter.

The suprarenal bodies were moderately congested. Some of the dilated venous channels contained fibrin clots, in the interstices of which were many Gram-positive rods, presumably an agonal bacterial invasion. The medulla was perhaps rather unduly "reticulated," but no neurofibromatous or other obvious lesion was detected.

As pathological changes in keeping with the general features of the disease were found in the neighbouring sympathetic ganglia, some analogous process might have been expected to occur in the suprarenal medulla, but of this we found no evidence. Our opinion as to this was kindly confirmed by Dr. H. W. C. Vines, to whom we submitted sections.

The pancreas and spleen showed nothing of interest apart from chronic venous congestion. In the liver, in addition to chronic venous congestion, there was some irregular patchy thickening of the capsule, and fibrosis passing in from its deeper surface in a few places surrounded and isolated small groups of liver cells, but there was no generalized cirrhotic process. A small lymph-node from the neighbourhood of the left suprarenal body contained dilated and proliferated cavernous spaces in its medulla, apparently both lymphatic and blood-vascular in nature, and perhaps analogous to the patches of vascular proliferation found in the central nervous system. In the retinæ there were no angiomatous or other tumours.

[1] In this connection the presence of fully formed and functioning Pacinian touch corpuscles in the actual substance of peripheral nerves is, as far as the authors' experience goes, a rare phenomenon, though common in many other situations such as in the walls of blood-vessels. In serial sections of the digital nerves and vessels of the right index finger of a female patient, aged 56, amputated by our colleague, Mr. Paterson Ross, for gangrene due to obliterative endarteritis, one of us (W. E. C. D.) found a well-formed Pacinian corpuscle situated in the interior of one of the lateral subcutaneous digital nerves at the level of the head of the first phalanx.

Case II.—F. C., male, aged 17, was first seen in November, 1933, complaining of occasional vomiting not associated with dyspepsia and unrelated to meals, and of rapid fatigue on attempting to walk.

Clinical history.—The illness had started three months previously. At first vomiting occurred almost daily, but became less frequent. His appetite remained good and he had not complained of headache or epigastric pain. He was stated to be able to walk normally for about 20 or 30 yards, after which he felt giddy and had occasionally fallen. For the past few weeks he had also experienced occasional diplopia after reading. No history of deafness or tinnitus was obtained. There was nothing of importance in his past history apart from pneumonia as a young child.

Family history.—His father died at the age of 50, of unknown cause. His mother was alive and well. Eight other children in the family were alive, healthy, and of normal stature. There was no history suggestive of neurofibromatosis or any similar disease in the family.

Condition on admission (November, 1933).—A somewhat undersized and poorly-nourished youth, looking about 12 years of age rather than his actual age of 17. There was some degree of infantilism and absence of pubic and axillary hair.

The pupils were equal, central, circular, and reacted normally and the fundi were normal. There was convergent strabismus owing to weakness of the right external rectus. Nystagmus appeared on lateral deviation to the left and right and also on looking upwards. There was partial nerve deafness on the right side. The functions of the other cranial nerves were normal, but speech was somewhat slurred.

All the intrinsic muscles of the right hand and the muscles of the right forearm were wasted and weak. There was slight inco-ordination of his right arm and tremor of the fingers. The right arm-jerks were brisker than the left. All movements of the lower extremities were possible, but there was slight general wasting of the muscles and bilateral pes cavus. The knee-jerks were brisk, the right slightly greater than the left. The ankle-jerks were moderate. Bilateral extensor plantar reflexes were obtained. The abdominal reflexes were present but sluggish. Sensation was apparently normal. He walked on a wide base and his gait was ataxic. The sphincters were unaffected.

Many scattered subcutaneous nodules and small fibroid masses were present over different parts of the body, e.g. back, calves, and in front of the right shin. They varied in size from that of a pea to that of an acorn. All were sessile and were firm to touch. They were not painful or tender. No *café au lait* patches were present. The heart and lungs were normal. The liver and spleen were not palpable. No enlarged lymph-nodes were felt. The pulse-rate averaged 80. The blood-pressure was 108/80.

Investigations.—The cerebrospinal fluid (November, 1933) contained two small lymphocytes per cubic millimetre; total protein was 0·28 per cent.; globulin was in moderate excess; the Wassermann reaction was negative; Lange, 3455432110. The blood Wassermann reaction was also negative. A blood-count showed no abnormality.

A biopsy of a subcutaneous nodule removed from the upper part of the back showed the structure of a fibroma with some degeneration of the fibres (H. C. Lucey).

Progress of the case.—The patient was transferred to the West End Hospital for Diseases of the Nervous System three months later (March, 1934). In addition to the previous symptoms, frontal headaches had appeared, there was increasing deafness in both ears and he was unable to walk without support.

Lumbar picture on April 6 (1934) showed a cerebrospinal fluid pressure of 220 mm., and Queckenstedt's test was positive. The fluid was slightly yellowish in colour and contained three small lymphocytes per c.mm.; total protein was 0·2 per cent.; globulin was in moderate excess and the Wassermann reaction was negative. The Lange curve was 3455432110.

On May 5 a large nodule was removed from the anterior tibial region of the right leg for biopsy. Microscopical examination showed a neurofibroma or fibroblastomatous tumour.

By the end of September further nodules, varying in size up to that of a broad bean, had appeared on the dorsum of the left forearm and also on the back, chiefly in the left scapular region and over the sacrum. By the end of the year (1934), papillœdema was present in both fundi to the extent of two dioptres. There was palsy of both 6th nerves and gross nystagmus. Bilateral ptosis was also present. The right side of the face was weak and the tongue deviated to the right on protrusion. The bilateral nerve deafness was more pronounced. Speech was practically unintelligible. There was a flaccid paralysis and muscular atrophy of the right arm and its deep reflexes were absent. Both arms were inco-ordinate. Both legs were considerably wasted, but the knee and ankle-jerks were exaggerated, the right being brisker than the left. Both plantar reflexes were extensor and the abdominal reflexes were absent. He was unable to walk, and his general condition was very poor.

During the next three months his condition slowly deteriorated, until by the end of March, 1935, he was completely aphasic, deaf, and helpless. His legs were now in a condition of flaccid paralysis with absence of both knee and ankle-jerks. The plantar reflexes, however, remained extensor.

Death occurred on April 17, 1935.

Autopsy.

The body resembled that of an emaciated boy of 12 to 14 years. Numerous subcutaneous swellings, varying in size from those just visible to the naked eye up to nodules the size of half a walnut were noted on the chest, back, abdominal wall and on the right shin. Two small pigmented moles of about 5 mm. in diameter and only slightly projecting were present, one on the chest and one on the back.

Cranium: The scalp contained no tumours. The skull-cap was thin and the indentations for the meningeal vessels were noticeably deepened. The dura was not adherent to the brain and no swellings were present upon its external surface. The brain was removed only with difficulty on account of

PLATE II.

FIG. 2.

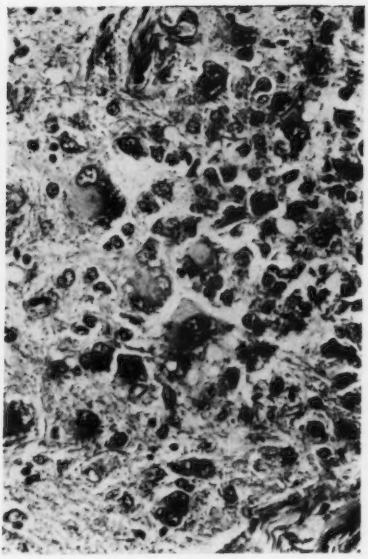

FIG. 4.

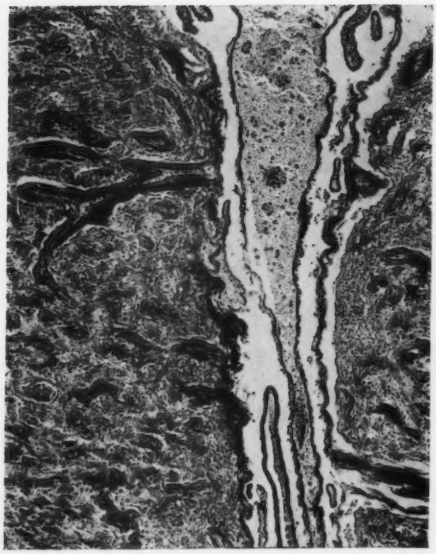

FIG. 3.

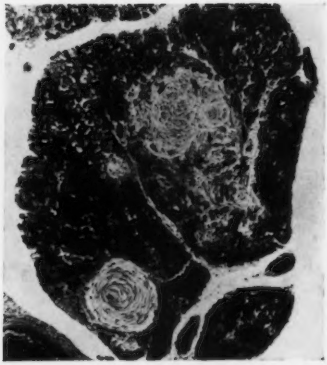

FIG. 5.

To illustrate paper by C. Worster-Drought, W. E. Carnegie Dickson, and W. H. McMenemey.

PLATE III.

FIG. 6.

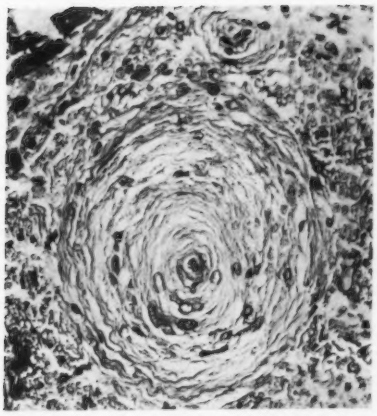

FIG. 7.

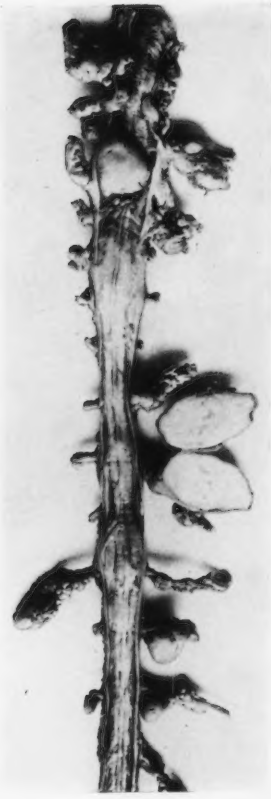

FIG. 8.

To illustrate paper by C. Worster-Drought, W. E. Carnegie Dickson, and W. H. McMenemey.

large masses which penetrated the base of the skull in relation to both auditory nerves and to the fifth nerve on the left side and extended into the petrous portion of the temporal bone on that side.

On each side of the superior longitudinal sinus the dura was adherent to the surface of the brain. On the deep aspect of the dura there were about twelve small hemispherical or ovoid flattened swellings, pale brownish-yellow in colour, with a finely granular surface and varying in size from 1 to 8 mm. in diameter; the largest was situated over the centre of the right frontal region.

Brain: This weighed 1,380 grm. Except for the comparatively slight indentations corresponding to the larger of the dural swellings the upper surface of the brain showed nothing of note. On the under surface were several swellings in relation to various cranial nerves, the largest, some 50 mm. in diameter, being at the right cerebello-pontine angle. The tumour was greyish in colour, slightly elastic to the touch and had a nodulated surface. On section, it was seen to consist mainly of a degenerate mass of semi-translucent dark grey material. A smaller tumour, about 18 mm. in diameter, was present at the left cerebello-pontine angle on the auditory nerve. It was irregular in shape with a "cauliflower-like" surface, and was intimately fused with the subjacent dura. This tumour was considerably harder to the touch than that on the opposite side.

The optic nerves throughout their course showed no swellings and appeared normal. On the left 3rd nerve was a tumour about the size and shape of an orange pip, and a similar though smaller tumour in the corresponding position on the right 3rd nerve. Numerous smaller swellings were present on the 10th 11th and 12th nerves of both sides, and on the left side two rather larger tumours probably also connected with those nerves. The tonsils of the cerebellum showed a well-marked pressure cone and the floor of the third ventricle was ballooned.

On horizontal section of the brain at the level of the pineal body, the third and lateral ventricles were found to be dilated and both foramina of Monro were considerably wider than normal. No ependymal granulations were present.

Spinal cord and nerve roots: Numerous tumours were present both upon the spinal nerve roots and within the spinal meninges (fig. 8). The largest of the latter was situated anteriorly and immediately above the level of the cervical enlargement. In shape, it resembled a flattened pebble, 17 to 18 mm. in diameter: it was attached in part to both dura and pia-arachnoid, and compressed and indented the spinal cord (fig. 9).

Many of the anterior and posterior spinal nerve roots, especially the latter, showed numerous small tumours, as many as a dozen upon a single root. Some of the nodules were only just visible to the naked eye, but most of them were about the size of a hemp seed, while others reached a diameter of 6 to 7 mm. On some of the posterior roots the tumours had developed at or near the posterior root ganglion; the largest of these was about the size of a broad bean. Although several of them projected into the intervertebral foramina,

none presented the typical dumb-bell shape often seen in spinal neurofibromata. The cauda equina contained numerous small tumours, but the filum terminale was free.

The spinal dura varied much in thickness over different parts of the cord, being stretched and thinned over the larger tumours and definitely thickened in other parts. On the posterior surface of the cord in the mid-dorsal region was a localized collection of cerebrospinal fluid shut off by adhesions. On section the cord seemed severely compressed in places by the tumours.

Peripheral nerves: Tumours visible to the naked eye and varying in size from that of a hemp seed to that of a broad bean were present upon the cords of the left brachial plexus, the right 8th and 9th intercostal nerves, the left

FIG. 9.—*Case* II. A low power magnification of the tumour compressing and distorting the cord in the cervical region. A small group of calcified psammomatous particles is visible near the distal edge of the tumour. (Celloidin section, Weigert-Pal. × 6.)

sciatic nerve, the right genito-crural nerve, and upon the right external cutaneous nerve of the thigh. The chain of swellings down the anterior aspect of the right leg was found on dissection to be superficial to the periosteum and apparently attached to a small superficial subcutaneous and not a periosteal nerve.

Other organs: Three tumours about the size of walnuts were lying in the mesentery. The lungs showed a patchy bronchopneumonic consolidation, particularly in the lower lobes, with purulent bronchitis and areas of collapse. The heart was small, its muscle pale and the valves healthy. The liver, spleen, pancreas, suprarenals and gastro-intestinal tract presented no unusual features, and there was no enlargement of lymph-nodes. No thymus was found. The thyroid body was normal in appearance, but the testes were small and undeveloped. There were no periosteal swellings. In neither of our

cases were there any of Masson's paronychial or "neuromyo-arterial glomus" tumours arising from the nail-bed, a series of which has been recently published by Purdy Stout (1935).

Histology.

Cerebello-pontine angle tumours.—Sections of the left cerebello-pontine angle tumour showed a variable degree of cellularity, a mixture of "whorls" and "palisading," the mixed feature already noted in Case I. Thin-walled vascular channels, sometimes distended with blood, occurred but were infrequent. Degenerative changes were not in evidence, but some degree of patchy œdema was noted. That part of the tumour adherent to the dura was a true "psammoma" with numerous and typical calcified particles each containing a central vessel or its remains undergoing hyaline degeneration. The intervening fibromatous cells, arranged in wisps and bundles and not infrequently in the characteristic parallel groups, were elongated and spindle-shaped; their diameters varied, but on the whole were narrow, giving them a wire-like appearance. In some parts the tissue was œdematous and in other areas hyaline degenerative changes had supervened.

The right cerebello-pontine angle tumour had undergone more extensive degenerative changes and was largely replaced by a "pseudocyst" containing semi-opaque amorphous and homogeneous dark gray material. The surviving peripheral tumour-tissue showed both varieties of cell arrangement with a varying degree of hyaline degeneration and œdema. No psammomatous particles and no hyaline vessels, such as were found in the corresponding tumour of the opposite side, were identified in the whorls. The central degenerated area consisted merely of amorphous and granular débris, enclosed within a delicate reticulum in which were scattered a few degenerating cell-nuclei. Vessels were very scanty.

With van Gieson's stain the cell bodies of both cerebello-pontine angle tumours showed the characteristic "terra-cotta" colour.

Gasserian ganglion.—On the left side this ganglion was adherent to the friable mass of growth arising from the 5th cranial nerve. Although no actual tumours were present in the Gasserian ganglion, there appeared to be in it some change analogous to tumour-formation. Proliferating cells formed small whorls around individual ganglion cells which were in varying stages of degeneration and disappearance.

Meningeal tumours.—The tumours arising from the arachnoid surface of the dura mater of the brain and cord were of meningiomatous type and were usually definitely psammomatous.

Cerebral cortex.—Histological examination of representative portions of the cerebral cortex failed to show any of the "meningio-angiomatosis" observed in Case I, nor did preparations impregnated by Cajal's gold sublimate method demonstrate any increase of astrocytes. Many of the smaller pial veins showed terminal septic thrombosis.

The choroid plexuses had undergone advanced "psammomatous" degeneration and resembled the changes seen in senility.

Spinal cord.—Many of the spinal cord tumours were "psammomatous" meningiomata and showed extensive hyaline degeneration and early calcification. In van Gieson stained preparations these meningiomatous tumours had not the terra-cotta colour characteristic of the acoustic neurofibroma. There was a possibility that some of them had arisen from posterior root ganglia, but many had developed from the inner or arachnoid aspect of the spinal dura. The majority, however, had originated from the anterior and posterior roots. Some of these tumours, especially those arising in close proximity to the cord itself, were of mixed type. In spite of extreme compression and distortion of the cord in many places, there was, as seen in Weigert-Pal preparations, remarkably little demyelination, as was also noted by Maas in his case of central neurofibromatosis.

Sympathetic ganglia.—No tumours were found on histological examination of the semilunar and other ganglia.

Sciatic nerves.—The right sciatic nerve showed no naked eye tumours, but when representative sections were examined microscopically, numerous minute tumours varying in diameter up to 1 mm. were found within it. These were moderately cellular, with a concentric laminated structure suggestive of that seen in some sensory nerve endings such as Pacinian touch corpuscles.

Pituitary body.—This organ was small, compressed and congested. Sections stained differentially showed the basophil, eosinophil and chromophobe cells in their usual and normal proportions.

Suprarenal bodies.—Except for slight congestion, these organs were normal, no neoplastic process being found in the medulla.

Mesenteric tumours.—These were neurofibromata containing both palisading and whorls, the former predominating.

Tumours in other parts.—The tumours arising from the left brachial and right lumbar plexuses, certain of the intercostal nerves, vagus nerves and the subcutaneous tumour of the abdominal wall, were all of essentially the same neurofibromatous type.

Discussion.

Ætiology.—Until comparatively recently no definite hypothesis could be put forward to account for the occurrence of multiple tumour syndromes. In 1931, Lindau in his paper on cerebellar cysts and their relation to angiomatosis of the retina (von Hippel's disease), referred to the angiomata and gliomata found in the walls of these cysts, and to their association with other congenital abnormalities often of a neoplastic nature. Some 20 per cent. of these cases are familial, and Lindau suggested that the syndrome which bears his name comes into the same category as tuberous sclerosis, and ascribed it to a loss of balance in the development of the mesoderm, beginning as early as the third month of embryonic life.

For some years past we have been of opinion that there is a distinct

relationship between a number of these syndromes characterized by multiple tumour formation, including not only Lindau's disease and tuberous sclerosis, but also neurofibromatosis and its variants, as well as the conditions associated with it, which we have enumerated and described in the present paper. We also include as analogous conditions a number of other multiple neoplastic syndromes, for example, myxo-chondro-adenoma of the base of the skull associated with cavernous angioma of the brain. A series of such multiple tumours from our hospital collection was demonstrated at the Dublin Meeting of the British Medical Association in 1933 (Carnegie Dickson); and Professor H. Bergstrand of Stockholm (1935), writing on "Sturge-Weber's Disease," which is characterized clinically by idiocy, paresis, epilepsy and visual disorders, and pathologically by cerebral hypoplasia and hypogyria, cortical calcifications, telangiectases of the pial vessels, buphthalmos and nævus flammeus of the face and other parts of the body, pointed out that these cases also come into the group now under discussion, and that incomplete variants, or *formes frustes*, of any of these may be found.

The application of recent work in Experimental Embryology, especially what has been termed "embryonic induction," throws considerable light upon the nature and origin of this group of multiple neoplastic diseases, the recent experimental work of Needham, Waddington and their colleagues being of special interest. The discovery by Spemann in 1918 that there is in the gastrula stage of the developing embryo an "organization centre" in the dorsal lip of the blastopore, the function of which is to stimulate the ectoderm of the embryo to give rise to the neural plate with its neural groove (becoming the neural canal), the notochord and the somites, was the fundamental experimental discovery upon which this new science has been founded. It has now been shown that the ectoderm of the area pellucida must be "competent" to react to this stimulus, and that the experimental implantation, say in the flank of the developing embryo, of a fragment of tissue containing living cells from this evocator centre can induce or evoke the development of a secondary or "parasitic" neural axis. Not only so, but a similar development can be induced by implanting the cells previously killed by boiling, or even by the use of an ethereal extract of them, the chemical substance involved being apparently of the nature of a sterol, i.e. a member of the chemical group which includes the antirachitic vitamins, the male and female sex-hormones, as well as œstrogenic, carcinogenic and other important stimulating or activating substances.

This extract from the dorsal lip of the blastopore is regarded as an organizer of the *first* grade, the function of which is to evoke the production of the primary axis of the embryo. There are also *secondary* evocators, which stimulate the formation of definite portions or "fields" of the embryo, e.g. a limb, an organ or part of an organ. Thus, as the optic cup grows out from the brain-vesicle and approaches the ectoderm, it induces in it the production of the lens of the eye. Similarly, the tympanic cartilage-ring stimulates the formation of the ear-drum. It has further been shown that the artificial implantation of eye-cup or cartilage—a fragment of any body cartilage will do equally well—will stimulate the production of eye-lens and ear-drum respectively in abnormal situations in the ectoderm, provided these latter are "competent," i.e. still possess sufficient formative capacity to show an active response. In other words, the tissue cells to be affected must also remain sufficiently "primitive," and must not have become too differentiated or "set" to respond to the appropriate stimulus. There is, in fact, what Needham calls a whole "hierarchy of organizers or morphogenetic hormones," of first, second, third and later order, coming into play one after the other as development advances, which stimulate and regulate the growth of tissues and organs.

It has also been discovered that these evocator substances exist, not merely in the region of the blastopore, but all over the egg, though in masked or inactive form, and may be freed and brought into play by being boiled and extracted, and then implanted in some "competent" part of the body of the developing embryo. Extracts not only of embryonic but also of adult tissues, such as mammalian liver, contain the needful sterol-like compounds and can act as evocators, some of them, however, apparently requiring to be activated by the presence or addition of nucleic, oleic or other higher fatty acid.

From this series of experiments it is but a step further to produce not normal, but pathological, forms of growth. Different parts of an organizer of the second or third order induce the formation of different organs, i.e. possess "individuating" properties which are related to the general plan of the whole body or the complete "individuation field" of the embryo. It is important also to discover how far this tendency persists in extra-uterine life and under what, if any, circumstances it may become perverted and pathological. Certain of the lower animals possess marked powers of repair, i.e. can bring these into play over an extensive "individuation field." A newt can regrow its tail, or a crab its claw or leg, but in man the powers of repair are relatively much

more restricted, though in the instance of, say, the erythroblastic or leucoblastic functions of the bone-marrow, very great expansion of this capacity is possible on the appropriate stimulation of the formative cells.

In the frog it has been proved that "over-ripeness" of the ova, i.e. if they are kept for a longer period than usual before they are fertilized, will cause many of them to give rise to the production of double monsters, or if kept longer still, to teratomatous tumours, which may be actively proliferative and often definitely malignant in character. This over-ripeness involves a disturbance of the metabolism of the sterols, and the development of secondary or parasitic embryos may be induced in the flanks or belly of the primary embryo just as they were by experimental implantation of evocator substances. Over-ripeness evidently acts in the same way as boiling, and liberates these substances indiscriminately. Under this stimulation the ectoderm may become thickened and undergo epitheliomatous development. In embryos in which the cerebral vesicles have already appeared, there may be various disturbances of second-grade induction, leading to deficiencies or malformations or to the production of tumour-like masses.

Needham points out that, with ova which under optimum conditions would produce, say 90 per cent. males, the first effects of "over-ripeness" are deviations in the sex-hormones: next the uncontrolled liberation of the evocators and the production of monsters or terata, and lastly the production of a carcinogenic agent and the development of teratomata—tumours in which malignancy in varying degree may supervene, the cells escaping as it were from the control of the "individuation field" and running wild as epithelioma or sarcoma. The production of teratomatous and teratoid tumours may be explained in Needham's phrase by "the possible permutations and combinations of irresponsible organizers and perversely competent tissues"; and he states it as his belief that "all further progress in unravelling these phenomena will depend upon our knowledge of the sterols."

Our present purpose has been to discuss whether these hypotheses may be applied to the elucidation of the problems involved in the multiple neoplastic syndromes, and we suggest that the manifold aberrent processes which we have described as occurring in our two cases may well be regarded as due to certain of these "permutations and combinations."

The evocators concerned in calling forth the formation of the covering and supporting framework of the nervous system are obviously the essential nervous elements themselves, the nerve-cells with their

cell-bodies and processes, more particularly the neuraxis-cylinder process itself, the nerve-fibre. These call forth a *parallel* arrangement of the cells of the nerve-sheaths whether derived as the lemmal cells from the neural crest and therefore of the nature of the peripheral glia, or from the neighbouring mesoblast as the connective-tissue cells of the epineurium investing the whole nerve-bundle.

Certain sensory nerve-terminals call forth around them the concentric whorls of Pacinian, Herbst and other forms of touch-corpuscles, the onion-like capsular tunics of which are formed by expansions of the connective tissue lamellæ of the perineurium or sheath of Henle.

These two sets of normal processes may become pathological, either because of some subtle change in the evocating nerve-elements, or from some perversion of the evocation field, mesoblastic connective tissue or glia as the case may be. The analogous palisades and concentric whorls of neurofibromatous and meningiomatous tumours, imitating the parallel structure of the supporting tissue of nerve-sheaths and the concentric capsules of touch-corpuscles respectively may be called forth by some chemical stimulus of perverted metabolism corresponding to the stimulus of sterol-containing boiled tissue or its ethereal extract, or the over-ripeness of ova. A point in favour of this argument is that the nerve-elements themselves—cells and fibres—are usually *absent* from the interior of these meningiomatous and neurofibromatous tumours.

Again the evocator may belong to the vascular system, and call forth the concentric psammomatous structure around the central choroidal capillary or around the arachnoidal villus in the meninges.

One need not elaborate the endless applications of this hypothesis. We may sum them up, as regards the multiple lesions of these neoplastic syndromes, as tissue-districts run wild, either because of some perversion in themselves or under the stimulus of some abnormal set of evocators, or perhaps to a varying combination of these two sets of factors—the details of the local lesions being brought about by the inherent tendencies of the tissues to carry out the original structural plans as component covering and supporting tissues of the nervous system.

As regards the hereditary factor, no positive family history was obtained in either of our cases. It is a well-established fact, however, that the disease is not infrequently both hereditary and familial (Preiser and Davenport, Christophe, Generisch, Minski, Cockayne, and Roger and Alliez).

The two cases here recorded appear to be of the same type as the case described by Wishart in 1822. One may regard them as being

examples of a mixed type of "fibroblastomatosis," the incidence of the neoplastic process being both meningeal and perineural.

It is not possible to differentiate this syndrome clinically from "central neurofibromatosis" ("central von Recklinghausen's disease"), unless it is possible to obtain biopsy specimens, as in Kernohan and Parker's case and in the first of our own two patients.

Other examples of the association of multiple meningeal and perineural tumours have been described by Soyka (1877), Langdon (1895), Henneberg and Koch (1903), Fraenkel and Hunt (1903), Kaulbach (1906), Westphal (1908), Verocay (1910), Leischner (1910), Christin and Naville (1920), Symonds (1921), Firket (1926), Hosoi (1930), Kernohan and Parker (1932), Katzenstein (1932), and by Shapland and Greenfield (1935).

In all of these the intracranial meningeal tumours were multiple. In the cases of Biggs (1909), Fleming and Cookson (1925) and Minski (1932), there was only one tumour attached to the cranial dura in each instance. In Regnier, Dechaume, Bourrat and Lesbros' case (1927) there were two meningeal tumours in association with those of the cranial nerves. Of Funkenstein's (1904) examples, Case 1 had bilateral acoustic nerve tumours, multiple neurofibromata, a "psammoma" and an "osteo-psammoma" of the spinal dura; whilst Case 3 had one acoustic tumour and one "psammosarkoma" of the dura. Flick's patient (1928) had numerous meningeal tumours and in addition a small mass in the left internal auditory meatus, and another, the size of a cherry-stone, on the left trigeminal nerve, both probably neurofibromata.

Multiple meningeal tumours, not associated with cranial nerve tumours, have been described by Schultze (1880)—only one of which was cranial, Schmidt (1902)—two cases, Henschen (1910), Heuer and Dandy (1916), Krivy (1926), Savy (1927), and Caspar (1927)—three cases. Cestan's patient (1903), on the other hand, had multiple cranial nerve tumours only.

Many but not all of the above have been associated with "peripheral neurofibromatosis" (von Recklinghausen's disease) of greater or lesser degree.

Acoustic nerve tumours in association with peripheral neurofibromata and neurofibromata of the cord in association with the peripheral disease, on the other hand, are relatively frequent in their occurrence and constitute the majority of cases of "central neurofibromatosis."

That we are dealing with variants of one disease has long been apparent, and Cornil (1933) has suggested the name "neuroectodermomatosis." This term has found favour with Roger and Alliez (1934), Agostini (1934) and others.

The nature of peripheral neurofibromatosis.—Although this condition (so-called "von Recklinghausen's disease") had been known for many years prior to the classical description in 1882 by von Recklinghausen himself, and had been admirably described and illustrated by Tilesius in 1793 and by Walther in 1814, it was not until some years later that an attempt was made to investigate the nature of the swellings. According to R. W. Smith, whose well-illustrated folio book (1849) may be consulted by those interested in the history of the subject, the term "neuroma" was introduced by Odier in 1803 to apply to a "tumour connected with nerve." Barkow (1829) was one of the first to recognize the importance of differentiating the case with solitary tumour from that suffering from the generalized disease; and Knoblauch (1844) went a step further in suggesting that the generalized disease resulted from "an original vice of conformation" and had no relation to the occurrence of solitary tumours. Smith (1849) and Virchow (1858) continued to term the tumour "neuroma," although the latter author realized that the majority were false or pseudo-neuromata. Von Recklinghausen (1882) considered these peripheral nerve tumours to be of fibrous tissue origin, an opinion which was shared later by Alexis Thompson (1900). Of the word "neuroma" it is interesting to recall that the latter said: "It is a convenient term, and employed in the clinical sense it indicates the most important feature of any particular tumour, viz. its seat in a nerve, irrespective altogether of its structure."

In 1910 the term "neurinoma" was introduced by Verocay to cover all the nerve tumours, both peripheral and central, in his case of the syndrome of Wishart. He considered that they arose from undifferentiated neurocytes which were normally capable of giving rise to sheath, ganglion and glial cells and under pathological conditions of growth could produce the corresponding type of tumour.

Valuable contributions to the histology of these tumours have been made by Durante, Antoni and by Penfield. The latter concludes that the presence of nerve fibrils within the tumours may be pathognomonic of neurofibromata, and that in this respect they differ from true "perineurial fibroblastomata." It would perhaps avoid confusion if we regarded the former as merely a more differentiated type of the latter.

The term "neur*in*oma"[1] has come to be applied only to the "solitary" type of nerve sheath tumour, but its use in this respect has been criticized by Stout (1935) on the grounds that it implies a nerve *fibre* tumour. He also dismisses the term "perineurial fibroblastoma" introduced by Penfield, and the two other popular alternatives "Schwannoma" and "peripheral glioma" as unsuitable. Stout suggests that this type of tumour be known as "neurilemoma." This word certainly has the advantage of terminological precision and does not attempt to do more than suggest the site of origin of the tumour.

In "peripheral neurofibromatosis," however, the tumours are nearly always incompletely differentiated and consequently fall strictly into the category of fibroblastomata. It seems certain that they can arise from the endoneurium, the epineurium, also presumably from the sheath of Schwann (the supposed origin of the solitary tumour) and the perineurium. In other words, they can theoretically, and often do, arise from any or all of the tissue elements connected with the nerves. They are, therefore, "perineural fibroblastomata" (not perineurial, a term which suggests an origin only in the perineurium).

The nature of acoustic nerve tumours.—Acoustic nerve tumours may be unilateral or bilateral, and may or may not be associated with other manifestations of "neurofibromatosis"—central, peripheral or a combination of both.

Minski (1932) concludes that bilateral acoustic nerve tumours with generalized peripheral neurofibromatosis are much more frequent than bilateral acoustic tumours alone, there being records of thirty-seven cases of the former syndrome and only seven of the latter. It would also seem that if acoustic tumours are associated with peripheral neurofibromatosis, the former are almost always bilateral. This is of interest, because it is stated by Cushing (1917) that for every case of bilateral acoustic nerve tumour (presumably uncomplicated by peripheral neurofibromatosis) there are 100 cases of unilateral tumour.

Acoustic nerve tumours were considered by Sternberg (1900) to be derived from an "anlage" of glial tissue. Cushing (1917) remarked on

[1] *Note.*—Neurinoma = Neur-in-oma. The Greek word *νεῦρον* meant originally a sinew or tendon; in the plural it came metaphorically to mean strength, *vireo* "nerves"; later it was applied to the fibres of plants; but not until Galen's time was it used to denote the physical nerves themselves (Liddell and Scott). The word *ἴς, ἰνός*, originally meant a muscle (at the back of the neck, *cf.* "*inion*"), and later came to mean a "fibre." The term "Inoma" was introduced by Paget for "Fibroma." "Neur*in*oma" therefore means a nerve-*fibre*-tumour.

† *Λέμμα*, a skin or sheath which can be peeled off (*λέπω* to strip or peel). Dr. Stout informs us that he believes it to be correct to spell this word with the single "m."

their similarity to the peripheral nerve tumours, noting that they differed only in their greater tendency to the formation of glia-like areas and in the absence or extreme rarity within them of nerve-fibres either with or without a myelin sheath. He considered that acoustic nerve tumours arose from undifferentiated cells at the junction of the glial elements with the sheath of Schwann. Skinner (1929), however, showed that the type-cell of the acoustic nerve tumour was the neurilemma-sheath cell, and he gave reasons for the belief that these cells exist in unusual numbers in the vestibular portion of the nerve, a view shared by Gardner and Frazier (1930). Penfield believes in their fibroblastomatous origin and emphasizes the importance of the identification of collagen fibrils in these tumours. The acoustic nerve tumours found in association with peripheral neurofibromatosis he considers to be of a different order, the presence of nerve-fibres within them being pathognomonic of neurofibromata and not of fibroblastomata, and he maintains that these fibres are found in cases of bilateral familial acoustic nerve tumours as well as in association with peripheral neurofibromatosis. Minski, however, was unable to demonstrate nerve-fibres in his case of bilateral familial acoustic nerve tumour, and similarly we have been unable to find them in our two cases except at the surface of the tumours, where they are obviously merely surviving fibrils of the original acoustic nerve. We ourselves are of opinion that acoustic nerve tumours, whether they occur singly, bilaterally or in association with peripheral or central neurofibromatosis, allowing for slight individual differences, are essentially similar in structure and of the nature of neurofibroblastomata.

The nature of meningeal tumours, and the association of "neurofibromatosis" with glioma.—The great majority of meningeal tumours occur singly, but, as has already been stated, instances in which they are multiple do occur, some eleven examples having been recorded. In association with peripheral and central neurofibromata, they are, however, practically always multiple, only three cases in which they are single having been described.

The term "meningioma" has been popularized by Cushing and Percival Bailey as being non-committal, for there is still considerable difference of opinion as to the exact histogenesis of these tumours. Some authors—Schmidt, Bailey, Bucy and Mallory—regard them as arising from clusters of arachnoidal cells. The view that they are fibroblastomata affords a satisfactory explanation of the variety of histological pictures which may be found. Cushing's view, however, is

that the meningoblasts are capable of differentiating into angioblasts, fibroblasts, and possibly other types of cell; the "meningio-angiomatosis" described in our first case appears to confirm this opinion.

Diffuse forms of meningeal tumour and "sarcomatous" changes were noted by Nonne (1902), Markus (1913), Bassoe and Shields (1916), Pirie (1919), Boyd (1925), Fried (1926), Moorhead and Wigham (1926), Connor and Cushing (1927), Bailey (1929), Learmonth (1929), by Froment, Dechaume and Christy (1930) and by A. H. Jackson (1933). Froment, Dechaume and Christy refer to the diffuse meningeal growths under the name of "Maladie d'Ollivier" (1825). Boyd noted tumour cells spreading along the perivascular prolongations of the subarachnoid space, and is of the opinion that the great majority of cases are secondary to neoplastic processes elsewhere. Moorhead and Wigham, under the term "meningitis carcinomatosa," described a diffuse endothelial growth over the cerebral cortex and the cerebellum, but they were unable to find a primary growth, permission for the examination of the viscera not having been granted. There is little doubt that many of the diffuse forms of growth are either metastatic and often carcinomatous in nature or are spreading medulloblastomata; nevertheless, there remains a proportion of cases which are probably of primary meningeal origin. Craig (1927) drew attention to the fact that intracranial endothelioma (i.e. what is now known as "meningioma") is not always benign, and Hosoi was able to collect sixty-five cases of "sarcomatous" degeneration of such meningeal tumours. Bailey made an interesting study of eight cases of intracranial sarcomatous tumours of the leptomeninges, all of different type, seven of which were apparently primary. Bailey and Bucy classified meningeal tumours into nine separate groups—mesenchymal, angioblastic, meningotheliomatous, psammomatous, osteoblastic, fibroblastic, melanoblastic, sarcomatous and lipomatous. Towne (1926) described invasion of the inferior longitudinal sinus by a meningioma of the falx cerebri, the process spreading into other venous sinuses; and we note the occurrence of multiple small meningiomata projecting into the superior sagittal sinus in our first case. Connor and Cushing (1927) described two cases—a male of 63 years, with a diffuse basal endotheliomatosis with tumour-cells originating from the adventitial sheath of blood-vessels; and a male of 11 years, with a surface gliomatosis, the cells being of the undifferentiated type as seen in a medulloblastoma.

Examples of the occurrence of gliomata in association with neuro-

fibromatosis have been collected by Strube (1898), Patoir and Raviart (1901), Henneberg and Koch (1903), Hulst (1904), Kaulbach (1906), Verocay (1910), Schnyder (1928), Dupouy, Courtois and Pichard (1929), Roger and Cremieux (1929), Stewart and Copeland (1931), and by Shapland and Greenfield (1935). Also, central tumours—the nature of which it was not possible to determine owing to the absence of post-mortem examination—have recently been reported in association with neurofibromatosis by Else (1933), Carrillo (1934) and Kanaar (1934). They are usually cerebral in origin, and Bailey states that they are frequently of the nature of polar spongioblastomata. We have recently seen an example of this type of tumour situated in the basal ganglia in a case of peripheral neurofibromatosis.

In a recent case of Roger and Alliez (1934), however, the cerebral tumour associated with peripheral neurofibomatosis was a glioblastoma multiforme. These writers also describe a case of diffuse meningeal gliomatosis resembling a medulloblastoma in a member of a family suffering from neurofibromatosis. Also, Foerster and Gagel (1934) described a "central diffuse Schwannosis" in association with this disease, the cells not being characteristic of spongioblasts, ependyma or microglia, but rather of sheath-cells. Martz (1933) noted a gliomatosis of the brain, spinal cord and pituitary body in a case of neurofibromatosis involving principally sympathetic ganglia, and Barber and Shaw (1922) have described the occurrence of a pituitary tumour.

That the peripheral nerve-tumours are capable of becoming malignant has been recognized for some time and Williams (1933) has reported a case of neurofibromatosis in which a "fibroma" of the sciatic nerve was removed and "recurred" as a spindle-celled sarcoma.

Generalized neurofibromatosis. — Penfield believes that "multiple neurofibromatosis" is a generalized fibrous connective tissue reaction involving both nerve-fibres and connective-tissue elements, the multiple manifestations depending upon the local cellular reaction peculiar to the tissue from which the tumour arises.

We are led to believe that this view is correct as far as it implicates the supporting tissue and that neurofibromatosis, both central and peripheral, is in part a dysplasia of the supporting tissue of the entire nervous system, both central and peripheral, but we are doubtful as to whether the nerve-elements themselves necessarily participate in the neoplastic formation. In the consideration of such tumours, we have found Adami's classification helpful, as it obviates the supposed difficulty of grouping together "pulp" or supporting tissue tumours derived from any of the three embryonic

layers. The term "Neurofibroblastomatosis"—or "Fibroblastomatosis of the nervous system"—covers all the numerous manifestations of the disease. We suggest, therefore, that until more is known of the subject, von Recklinghausen's disease should be considered pathologically as a neurofibroblastomatosis.

As the majority of the tumours are on nerves or meninges, the following classification of the main varieties of the disease may be formulated. It should be remembered, however, that glial tumours may complicate all varieties of the disease.

Main varieties of neurofibroblastomatosis.—A. Central Type: (1) Meningeal and Perineural—Syndrome of Wishart (1822)—rare. (2) Meningeal only—Syndrome of Schultze (1880)—rarest. (3) Perineural only—Syndrome of Knoblauch (1843)—commonest. B. Peripheral type: Peripheral neurofibromatosis or von Recklinghausen's disease (1882) first described by Tilesius in 1793.

Types A and B are not infrequently combined. There are many subvarieties of (1) and (3) of Type A, but it serves no useful purpose further to subdivide them.

Any of these types may be associated with a greater or lesser degree of malignancy in their individual tumours, and this is a further reason for regarding them as variants of one disease—neurofibroblastomatosis.

In addition there are other and allied pathological processes with which the condition may be associated.

The association with and relation to syringomyelia.—Several authors have noted the occurrence of a syringomyelic cavitation of the spinal cord in association with neurofibromatosis, viz. Patoir and Raviart (1901), Castronuovo (1920), and Kernohan and Parker (1932). Katzenstein (1932) has reported an ependymal reaction and hydromyelia.

In both our examples there was in the spinal cord cavitation and an ependymal reaction, most marked in Case I. Such cavitation may be a secondary phenomenon due to compression and distortion of the cord and to the impoverished blood-supply. On the other hand, since syringomyelia itself is a disease of presumably similar developmental origin, it is natural to regard the association as not merely fortuitous. In this connection it is interesting to note that acromegaloid tendencies have been described in both diseases. We can find no record, on the other hand, of the clinical entity known as "syringomyelia" being complicated by neurofibromatosis, either peripheral or central. It would seem best for the present, therefore, to regard the question of the possible relationship of the two diseases as unsettled.

The association with and relation to tuberous sclerosis.—This disease has been fully described, within recent years, by Critchley and Earl (1932). Orzechowski and Nowicki (1912) recorded the case of a male, aged 18, with the typical post-mortem findings of tuberous sclerosis, combined with many of the features of peripheral and central neurofibromatosis. Other authors have described similar associations (Gamper, Urbach and Wiedman, and Rump), and in a review of the subject Critchley is in favour of regarding the two diseases as closely related, a view also put forward by one of us (W. E. C. D., 1933).

In connection with the investigation of our two cases, we wish to express our thanks for the skilled technical assistance given us by Messrs. John Ottewill and Charles Martin.

Summary.

(1) Two cases are recorded of multiple tumours of the nervous system—meningeal and perineural—with associated and analogous changes in glia and ependyma.

(2) The clinical manifestations consisted of multiple cranial nerve lesions, including bilateral nerve deafness, ocular palsies, nystagmus and papilloedema; speech difficulties; a combination of upper and lower motor neurone paresis of the limbs and bilateral pes cavus. In one case subcutaneous neurofibromata were numerous, but in the other only one such tumour—on the back—appeared. The cerebrospinal fluid of both cases showed Froin's syndrome. The disease in the first case lasted eight years, and in the second one year and eight months.

(3) Histologically, the tumours varied from frank meningioma to typical neurofibroma, depending upon the site of origin, those arising from meninges tending to be psammomatous, those from nerve-sheaths neurofibromatous. Admixtures of the two types occurred in areas where a double origin was possible, e.g. the cerebello-pontine angle tumours and certain of those arising in relation to the spinal cord. Analogous changes in the glia and ependyma, and also syringomyelic cavitation were present in the spinal cords of both cases.

(4) The association of multiple meningeal and perineural tumours is infrequent and was first described by Wishart in 1822. This "Syndrome of Wishart" is one variety of "neurofibromatosis."

(5) The disease from the pathological standpoint might more accurately be described as "neurofibroblastomatosis." The term "von Recklinghausen's disease" should be confined to the purely peripheral subcutaneous form of the disease.

(6) The probable bearing of recent experimental work in inductive embryology upon the general problem of multiple neoplastic syndromes is discussed.

(7) A clinical classification of the different forms of "neurofibroblastomatosis" is suggested and an account of the pathological variants is given.

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LEGENDS FOR PLATES II AND III.

FIG. 2.—*Case* I. Cerebral cortex from the posterior part of the right middle frontal convolution. The cortex is the seat of a meningio-angiomatous condition. The subjacent white matter has the curious fenestrated appearance described in the text. (Weigert-Pal. × 2½ diam.)

FIG. 3.—*Case* I. Cerebral cortex involved in meningio-angiomatosis. A mixed meningiomatous and angioblastic condition invading the grey matter from the surface. Note the proliferation of the vessels of the leptomeninges in the sulcus and their penetration inwards along with meningiomatous cells. (Mallory's connective tissue stain. × 32.)

FIG. 4.—*Case* I. Cerebral cortex. Gliomatosis in a meningio-angiomatous area. Note the proliferated glial cells; some of them are multinucleated and resemble the abnormal glial cells seen in tuberous sclerosis (the so-called "Gemästetezellen"). (Hæmatoxylin and Eosin. × 400.)

FIG. 5.—*Case* I. Transverse section through a lumbar posterior nerve root showing concentric whorls reminiscent of a meningioma; a similar tumour found upon the sciatic nerve will be seen in fig. 7. (Weigert's Hæmatoxylin and van Gieson. × 100.)

FIG. 6.—*Case* I. Lumbar cord showing extensive central gliosis with cavitation expanding and distorting cord. There is only a slight amount of demyelination. Note the small neurofibroma on a posterior nerve root. (Weigert-Pal. × 10.)

FIG. 7.—*Case* I. High power. Transverse section through sciatic nerve showing the formation of a minute concentrically arranged nodule of tumour similar to those found in many of the spinal nerve-roots. In its structure it is distinctly reminiscent of a Pacinian touch-corpuscle. (Hæmatoxylin and Eosin. × 400.)

FIG. 8.—*Case* II. Ventral aspect of the cervical and dorsal cord showing multiple tumours. The large tumour just above the cervical enlargement is seen compressing the cord.

BERGER'S *a* RHYTHM IN ORGANIC LESIONS OF THE BRAIN.[1]

By FREDERICK LEMERE, M.D.
Psychiatrist, Eastern State Hospital, Medical Lake, Washington.

It is now generally recognized that the electrical potential changes occurring in the brain at different frequencies may be picked up from the intact scalp and recorded by means of the oscillograph. By far the most outstanding rhythm is that which has a rate of around ten waves per second (Berger's alpha waves [1]). This rhythm is present in the vast majority of cases only when the subject is at rest with his eyes shut. It seems fairly certain that the waves are produced by groups of cells beating in unison in the occipital lobe (Adrian *et al.* [2 and 3]). As soon as the subject opens his eyes and focuses on an object, the occipital cortex is no longer free to beat spontaneously and the rhythm breaks up and disappears.

The purpose of this paper will be the study of the effect of various cerebral lesions on the *a* rhythm. Only passing attention will be paid to the other less obvious cerebral rhythms as their nature and significance are still obscure.

Material and Methods.

Electroencephalograms were obtained from fifteen normal subjects and sixty patients with intracranial cerebral lesions. Each subject was examined on from three to five separate occasions at intervals of from one to seven days. A balanced input amplifier was used in conjunction with a Matthews ink-writing oscillograph.

The electrodes were gauze pads moistened with saline solution and placed against the scalp, one in front and the other at the back of the head. The rhythm from the two cerebral hemispheres was compared by taking several recordings alternately from the two sides of the head. In all the normal control records, the waves from the right side of the

[1] This work was financed by a grant from the Rockefeller Foundation and carried out at the National Hospital, Queen Square, London. I wish to express my sincere gratitude to the staff of this hospital for enabling me to work there.

The diagnoses of the cases used in this investigation were made by the staff and were confirmed by autopsy, encephalography, or operation in 80 per cent. of the cases.

head were equal in height, regularity and frequency to those from the left side of the head (fig. 1).

The instructions were for the patients to lie as quietly and as relaxed as possible and to open and shut their eyes as requested. Only those who could co-operate with this procedure were used in this investigation

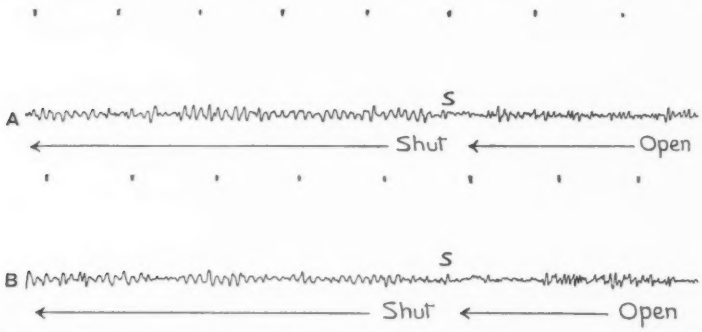

FIG. 1.—Representative sections of a record taken from a normal control subject showing the similarity of the Berger rhythm on the two sides. Time in seconds. Eyes shut at S. (A) Right side. (B) Left side.

BERGER'S *a* RHYTHM IN UNILATERAL LOCALIZED CEREBRAL LESIONS.

The following cases presented the opportunity of observing the changes in the *a* rhythm produced by the lesion on the affected side as opposed to the normal rhythm from the opposite or unaffected side. In some cases, the pathological rhythm varied from time to time, and it was considered absolutely necessary to make repeated observations before drawing any final conclusions.

Frontal lobe lesions.—Four patients were examined; one had an abscess without increased intracranial pressure, the second a tumour with increased intracranial pressure, and the third and fourth tumours without increased intracranial pressure. All but the first case showed a slightly stronger rhythm on the affected side, i.e. the waves were larger and more often present.

Parietal lobe lesions.—Three cases were examined; all were tumours, but only the third had increased intracranial pressure. The Berger rhythm again was slightly stronger on the affected side, except in the first case where the rhythm on the two sides was equal.

Deep temporal lobe lesions.—Only one case, presenting occasional uncinate fits, was observed. The *a* waves on the affected side were much stronger than on the normal side.

Parieto-temporal lobe lesions interrupting the optic radiations.—Four such cases were studied—all due to tumour. Two had increased and two had normal intracranial pressure. The *a* waves were more

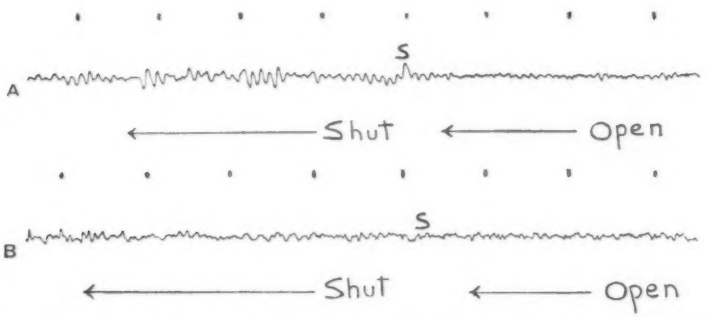

FIG. 2.—Representative sections of a record obtained in a case presenting practically complete right-sided hemianopia due to a two-year-old thrombosis of the left posterior cerebral artery. Time in seconds. Eyes shut at S. (A) Right or normal side. (B) Left or affected side with no true Berger rhythm.

pronounced on the affected side and in two, where the hemianopia was complete, the rhythm was present on the affected side with the eyes open or shut. In other words, the lesion so isolated the visual cortex

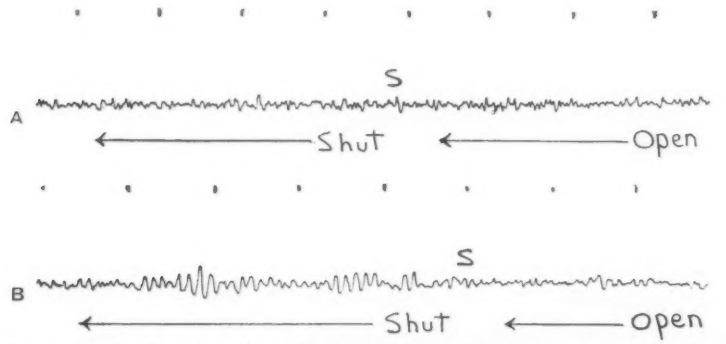

FIG. 3.—Representative sections of a record taken from a patient with a right sided basal ganglion lesion. Time in seconds. Eyes shut at S. (A) Left or normal side. (B) Right or affected side showing a markedly augmented Berger rhythm.

from the incoming visual impulses on the affected side that a spontaneous rhythm was free to develop with the eyes open or shut.

Occipital lobe lesions (fig. 2).—Four patients were observed: one had a cyst involving the lobe on one side, the second a tumour without

associated increased pressure, and the third and fourth suffered from thrombosis of the posterior cerebral artery. The Berger rhythm was absent on the side of the lesion in the first three cases where the

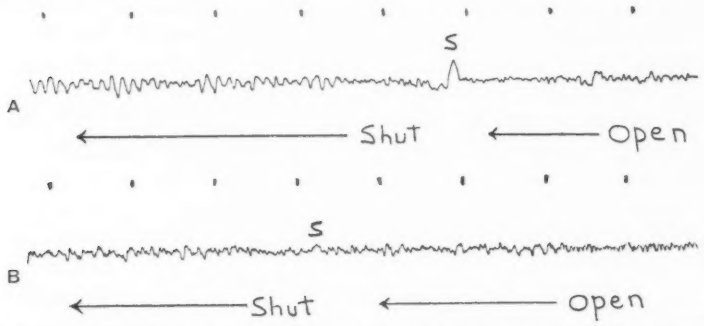

FIG. 4.—Representative sections of a record from a case presenting a thalamic syndrome on the left (lesion in the right cerebral hemisphere). Time in seconds. Eyes shut at S. (A) Left or normal side. (B) Right or affected side showing a depression of the Berger rhythm.

hemianopia was fairly complete. In the fourth case there was only a partial hemianopia and the Berger rhythm was present, but much depressed, on the affected side.

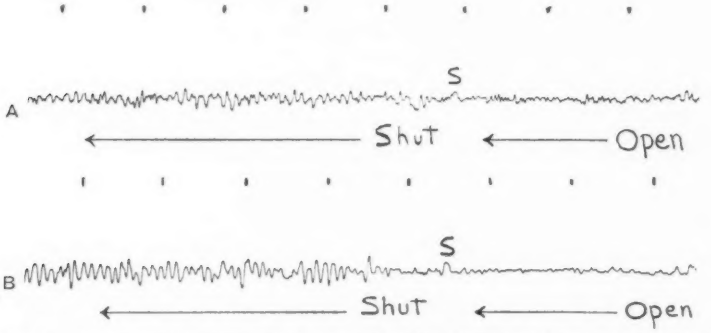

FIG. 5.—Representative sections of a record taken from a patient with a right sided fronto-parietal cortical atrophy. Time in seconds. Eyes shut at S. (A) Left or normal side. (B) Right or affected side showing an augmentation of the Berger rhythm and a depression of the beta (20 per second) waves which are most easily seen when the eyes are open.

Basal ganglion lesions (fig. 3).—Three cases presenting signs of unilateral basal ganglion lesions and loss of function were studied. In all three there was a markedly better *a* rhythm on the side of the lesion.

Thalamic lesions (fig. 4).—Five cases with a typical "thalamic"

syndrome on one side were observed. The first four were apparently due to cerebral vascular lesions in the region of the thalamus and internal capsule, while the fifth was produced by a tumour in the region of the mid-brain and hypothalamus. The rhythm was depressed on the side of the lesion in all but the first case where the two sides were equal.

Cortical atrophy.—Three cases of long standing unilateral cortical atrophy were observed. The atrophy in the first case included only the frontal and parietal lobes and the *a* rhythm was increased on the affected side (fig. 5) ; in the other two, however, the atrophy included the whole hemisphere and there was an associated hemianopia. In these two cases, the *a* rhythm was very much depressed on the affected side.

Cerebellar lesions.—Two cases of tumour with mildly increased intracranial pressure were studied. No difference between the *a* rhythm from the two sides of the head was noticed.

Berger's *a* Rhythm in Bilateral and Generalized Cerebral Disease.

Pituitary tumour (fig. 6).—Two cases of tumour without increased intracranial pressure were observed, and in both there was severe amblyopia. The *a* rhythm was equally present on both sides and was almost as strong with the eyes open as with the eyes shut.

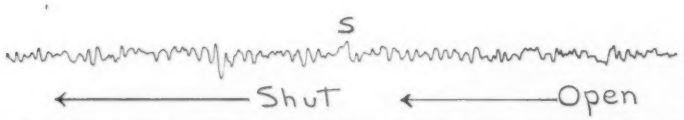

Fig. 6.—Representative section of a record taken from a patient with pituitary tumour and resulting amblyopia. Time in seconds. Eyes shut at S. Shows the Berger rhythm present with the eyes open or shut.

Bilateral lenticular disease.—Three cases of Wilson's diseases were examined. The *a* rhythm was strong in the least affected patient and less obvious in the most deteriorated one. One case of postencephalitic Parkinsonism was observed. The rhythm was apparently normal in this case.

General paresis.—Six patients were studied representing both acute, chronic, and arrested stages of the illness. In all the rhythm was rather weak.

Cerebral arteriosclerosis.—Seven cases were studied and all showed

a rather poor *a* rhythm except for one patient with a history of several manic-depressive attacks [4].

Organic dementia.—Seven cases were observed, including three deteriorated epileptics, one diffuse sclerosis, one progressive muscular atrophy, one disseminated sclerosis, and one olivo-ponto-cerebellar disease. In all the *a* rhythm was rather poor.

Miscellaneous Observations.

The normal range of Berger's *a* rhythm is between 9 and 12 beats per second [4]. In none of the cases with unilateral lesions was there a noticeable difference between the rhythm rate on the affected and on the normal side. In those cases with dementia, markedly increased intracranial pressure, and paraldehyde, morphine, or bromide intoxication, the rate was definitely on the low side, running around 7 to 8 beats per second. Berger [5] has described a slowing of the alpha waves to from 3 to 5 per second in these conditions and such waves are certainly seen. I do not believe, however, that these slow waves are modified Berger's alpha waves as they are present with the eyes open or shut.

Berger has recently stated [6] that in acute paretics the rhythm is irregular with shorter 12 to 18 per second waves interspersed amongst the regular 9 to 12 per second waves. He believes that this denotes an irritative process in the cerebral cortex and that in arrested paretics the rhythm becomes more regular. I have also noticed this irregularity in paretics, but have seen it occasionally in other conditions as well, such as mental deficiency and senility.

The nature of Berger's beta waves (those occurring at a rhythm of around 20 per second and over with the eyes open or shut) is not well understood. They seemed to be depressed the most by lesions involving the parietal lobe. In a case of complete unilateral cortical atrophy the unaffected side showed a normal rhythm, while the atrophied side showed no alpha or beta waves, but many 3 to 5 per second waves with the eyes open or shut. This suggests that the alpha and beta waves come from the cortex, while the slower 3 to 5 per second waves arise either from an organically affected cortex or subcortical centres [7].

Out of seven patients with Jacksonian fits from localized cerebral lesions, five showed sporadic spikes of relatively high voltage (fig. 7). These represented a positive potential applied to the electrode nearest the area of the lesion. There was no evidence of any convulsive phenomena at the time of these sporadic outbursts of relatively high potential. Such spikes have been described by other workers [8].

Records were obtained during migraine attacks in two subjects. The only alteration observed was a suppression of the Berger rhythm during the visual aura, but not during the subsequent period of headache. This suggests that the mechanism of migraine is fundamentally different from that of epilepsy where there are definite electrical discharges characteristic of an attack [9].

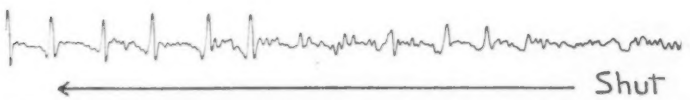

FIG. 7.—Representative section of a record from the right side of a patient with Jacksonian fits originating in the right occipital lobe. Time in seconds. Eyes shut. Represents positive potentials sporadically applied to the posteriorly placed electrode (that placed nearest the discharging focus). No signs of convulsion or visual aura.

Two cases of unilateral Horner's syndrome were observed and no difference noticed in the rhythm from the two sides. Apparently the sympathetic nerve supply to the brain has nothing to do with the activity of the cerebral cortex, at least in regard to the production of the Berger rhythm.

DISCUSSION.

It is recognized that the material presented is quite insufficient for the drawing of any final conclusions. It does, however, offer certain leads for further work and already seems to have been of some value in diagnosis. For example, in cases presenting hemianopia, and in which there is doubt as to whether the optic radiations or the occipital lobe itself is involved, a strong α rhythm would suggest the former while a weak or absent rhythm would favour the latter diagnosis.

In some cases a diagnosis between a frontal lobe lesion on one side or a cerebellar lesion on the opposite side presents difficulties. A difference between the two sides (especially a slightly better rhythm on the affected side) would suggest a frontal lobe lesion.

The value of potential records in the investigation of different forms of epilepsy has been discussed by Berger and recently by Gibbs and Lennox.

SUMMARY AND CONCLUSIONS.

Electroencephalograms were obtained from the two sides of the head in fifteen normal subjects and in sixty patients with intracranial lesions. In the normal subjects and in those patients with bilateral

generalized cerebral lesions, Berger's *a* rhythm (that occurring at 10 per second with the eyes shut) was the same on the two sides.

Unilateral localized lesions of the frontal, parietal, or temporal lobes were associated in general with a slightly stronger rhythm on the affected side. Basal ganglion lesions resulted in a very much stronger *a* rhythm on the affected side while thalamic and hypothalamic lesions depressed the rhythm on the affected side.

Fairly complete lesions of the occipital lobe on one side resulted in a very poor or absent rhythm on that side. Lesions of the optic radiations, on the other hand, were associated with a strong *a* rhythm on the affected side which was even present with the eyes open, provided the hemianopia was fairly complete.

The suggestion of Adrian and Matthews that the *a* rhythm is produced in the cortex of the occipital lobe seems to offer the best basis for the interpretation of the effect of these unilateral lesions. Any lesion tending to isolate, but not involve, the occipital lobe caused a strengthening of the rhythm on the affected side. Any lesion involving the greater part of the occipital lobe, on the other hand, produced an almost complete absence of rhythm on the affected side. The depressing effect of thalamic lesions on the *a* rhythm on the affected side is less easily understood and requires further investigation.

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[3] ADRIAN, E. D., and YAMAGIWA, K. "The Origin of the Berger Rhythm," *ibid.*, 1935, **58**, 323.

[4] In an article in *Brain*, 1936, **59**, 366, I have pointed out that manic-depressive patients have a much stronger Berger rhythm than schizophrenic patients.

[5] BERGER, HANS. "Ueber das Elektrenkephalogramm des Menschen," *Arch. f. Psychiat.*, 1932, **97**, 6.

[6] *Idem.* "Ueber das Elektrenkephalogramm des Menschen," *ibid.*, 1936, **104**, 678.

[7] With the method used in this investigation these slow waves were not seen in normal people. They have been described, however, by several authors as occurring during normal sleep.

[8] JASPER, H. H., and ANDREWS, H. L. "Human, Brain Rhythms: I, Recording Techniques and Preliminary Results," *Journ. Gen. Psychol.*, 1936, **14**, 98.

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THE CORTICAL PROJECTION OF THE PULVINAR IN THE MACAQUE MONKEY.

BY W. E. LE GROS CLARK AND D. W. C. NORTHFIELD.
(Department of Human Anatomy, University of Oxford.)

THE view is generally held that the pulvinar, which forms the posterior pole of the thalamus, projects on to that part of the parietal lobe which lies closely adjacent to the visual cortex. In 1933 and 1934 (Clark and Boggon, 1935) a series of experiments were carried out with the object of defining the thalamo-cortical connections in the macaque brain by the study of cellular atrophy in the thalamus following localized cortical lesions. It was found that, with lesions placed in different parts of the parietal lobe, very little secondary atrophy in the pulvinar ensued. It was assumed that, unless its projection on to the cortex is distributed very diffusely, the main element of the projecting pole of the pulvinar has little, if any, direct connection with the parietal cortex. On the other hand, evidence was brought forward which indicated that the intergeniculate nucleus of the pulvinar (element *pd* of Friedemann) projects on to the periparastriate areas of the cortex—that is to say, Brodmann's areas 18 and 19. These results were held to be consistent with Poliak's conclusion (1932), based on Marchi studies, that very few fibres from the pulvinar reach the cortex. However, in 1935, there appeared a report by Earl Walker of the cell degeneration in the thalamus following complete hemi-decortication in two monkeys. In one case all the cells of the pulvinar had undergone complete atrophy, while in the other the pulvinar had "practically completely degenerated." These results must be taken to indicate that at least the greater part of the pulvinar does in fact project on to the cerebral cortex. Since most of the parietal cortex has been excluded on the basis of cell degeneration experiments as the destination of these projection fibres (except those arising from element *pd*), it remains to be determined what are the cortical connections of the main element of the pulvinar. A clue was provided to this problem in the course of some experiments recently undertaken for the study of the thalamic

connections of the temporal lobe (Clark, 1936). It was found that lesions involving the middle part of the superior temporal gyrus and the lips of the Sylvian sulcus were followed not only by retrograde cell degeneration in the medial geniculate body, but also by a well-defined patch of atrophy in the main element ($p\beta$) of the pulvinar. It was concluded, on the basis of these observations, that "the pulvinar projects, in part at least, on to the posterior Sylvian receptive region of the cortex"—a region which Poliak (1932) first described as extending back from the auditory area along the walls and lips of the Sylvian sulcus as far as its caudal extremity.

The present experiments have been designed with the purpose of clearing up the doubtful points which remain in regard to the cortical projection of the pulvinar. In the first experiment the whole of the parietal lobe on the lateral surface of the cerebral hemisphere was removed in order to define the maximum relation between the cortex of this lobe and the pulvinar. In the second case the cortical ablation was limited to the whole extent of the posterior Sylvian receptive area. Lastly, in two monkeys portions of areas 18 and 19 were removed in order to test the suggestion previously made that this part of the cortex receives fibres from the intergeniculate nucleus of the pulvinar.

Methods.

As in previous experiments of the same kind, the operations were performed under nembutal anæsthesia. The cerebral hemisphere was exposed by raising an osteoplastic flap, and the cortical lesion was made with the aid of an endothermy apparatus. The animals were kept for approximately six weeks, after which they were sacrificed by an overdose of chloroform. On removal of the brain the lesion was measured and its appearance reproduced to scale in a free-hand drawing. The cortical lesion and the corresponding half of the thalamus were sectioned and stained with Borell's methylene blue. Representative sections of the thalamus were traced by means of a projection apparatus, with the delineation of the various nuclear elements and the area of cell atrophy. In all cases the area of atrophy was well defined and quite sharply circumscribed. A photomicrograph of one of these degenerated areas (from Experiment A) is shown in Plate IV, fig. 1, to indicate the degree of their definition. The nomenclature of the nuclear elements of the pulvinar used here is that employed by Friedemann in his photomicrographic atlas of the cercopitheque thalamus published in 1911-12.

Experimental Results.

Experiment A.—O.M. 113. Operated December 19, 1935, killed February 19, 1936.

In this case an extensive ablation of the parietal lobe of the left cerebral hemisphere was made. The animal made a very rapid recovery from the operation. For a few days it showed a marked weakness of the right arm and leg, but within a week of the operation this paresis had disappeared and the animal's movements appeared quite normal.

Immediately after death the brain was removed and the extent of the lesion reproduced as accurately as possible in a diagram (fig. 1A). Superficial examination showed that it had involved almost the entire parietal lobe except for a narrow strip of cortex along the caudal lip

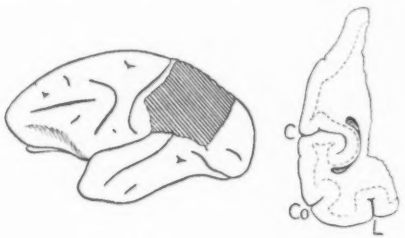

Fig. 1A. Fig. 1B.

Fig. 1A.—The cortical lesion in Experiment A. × ½.

Fig. 1B.—Coronal section through the middle of the lesion in Experiment A. × 1. *C.*—Calcarine sulcus. *Co.*—Collateral sulcus. *L.*—Lower end of lunate sulcus.

of the central sulcus. Above, the lesion just reaches the upper margin of the hemisphere. Behind it involves the anterior lip of the occipital operculum in its dorsal half. The lower extremity of the superior lunate sulcus can be seen emerging from the postero-inferior angle of the lesion. The lower border of the lesion lies on a level with the inferior extremity of the central sulcus, and it extends forwards involving the upper buried surface of the superior temporal gyrus as far as the posterior end of the insula. The rostral border of the lesion reaches to within 2 mm. of the central sulcus at its upper end, and 7 mm. at its lower end. The whole lesion measures 23 mm. in its antero-posterior extent and 30 mm. in vertical diameter.

Figure 1B shows a drawing of a vertical section through the middle of the lesion. It will be noted that the lesion extends deeply into the white matter, encroaching on the dorsal half of the optic

PLATE IV.

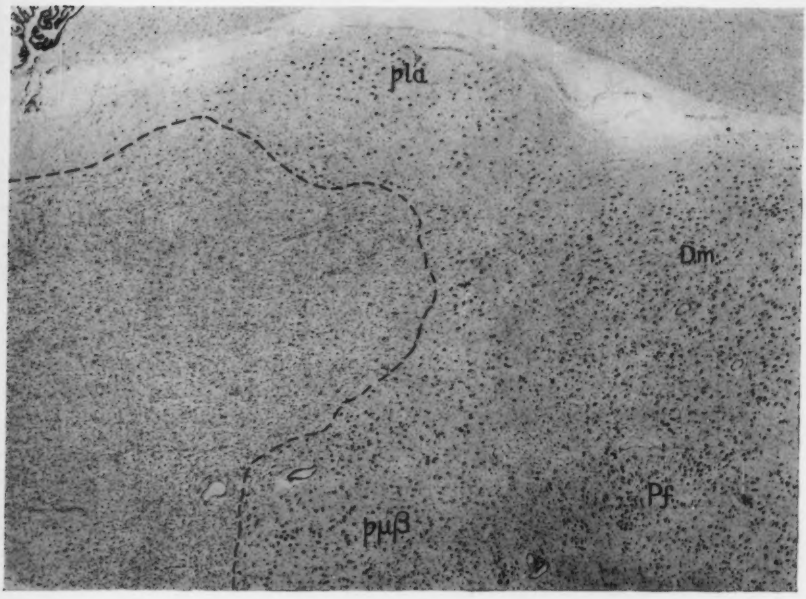

FIG. 1.—Transverse section through the pulvinar in Experiment A, showing the area of cell atrophy to the left. × 28.

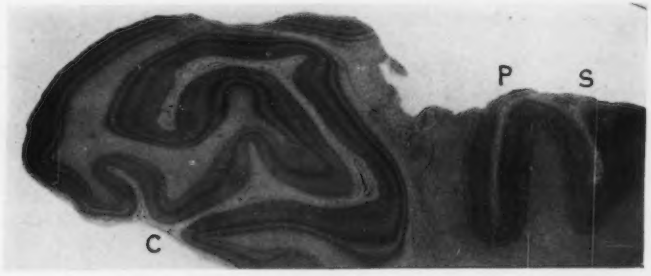

FIG. 2.—Antero-posterior section through the middle of the lesion in Experiment C. *C.* Calcarine sulcus. *P.* Parallel sulcus. *S.* Sylvian sulcus.

To illustrate paper by W. E. Le Gros Clark and D. W. C. Northfield.

radiations close to the lateral aspect of the posterior horn of the lateral ventricle. It also involved the peristriate areas and the rostral border of the area striata, and also almost all the area post-centralis except that part which lies buried in the posterior wall of the sulcus.

The thalamus.—Serial sections through the length of the thalamus show considerable areas of complete cell atrophy accompanied by a dense gliosis. For descriptive purposes these sections may be traced in a rostral direction. The first section of the first block passes through the extreme tip of the projecting pole of the pulvinar. In section 120 a small patch of cell atrophy and gliosis appears at the dorso-lateral angle of the pulvinar where it comes into continuity with the internal capsule. Sixteen sections later, the first block comes to an end. Here the patch of complete cell degeneration is very distinct, and from it a zone of gliosis and partial cell atrophy extends for some little distance into the centre of the pulvinar and medially along its dorsal surface, involving Friedemann's elements $p\beta$ and $p\mu$ (fig. 2*b*).

The first section of the second block cuts through the middle of the medial geniculate body, the base of the main element of the pulvinar $p\beta$, the intergeniculate nucleus, the posterior commissure, and the habenular ganglion. At this level most of the pulvinar had undergone complete secondary degeneration. The portions which are left intact comprise a strip along the medial border of element $p\beta$, the most ventral part of $p\mu$, the whole of *pa*, and the intergeniculate nucleus (fig. 2*c*). There is also a thin row of normal cells along the dorsal surface of the pulvinar. A corresponding extent of the nucleus reticularis has also undergone atrophy. The medial geniculate body at this transverse level is quite normal, and no definite signs of cell degeneration or gliosis could be detected in the pretectal nucleus. It is to be noted that there is a very sharp line of demarcation between the atrophic zone and the normal elements. A few sections further forwards, the atrophic area extends ventrally into the upper border of the intergeniculate nucleus, *pd*. At Section 60, the posterior ends of the parafascicular and dorso-medial nuclei and the caudal extremity of the lateral half of the lateral geniculate body appear. All these elements are normal here. Practically complete cell degeneration involves the caudal ends of the lateral nucleus and the pars externa of the ventral nucleus. A group of normal cells lies close against the medial medullary lamina, representing a portion of element $p\mu\beta$ of the pulvinar. Element *pla* is also intact. More ventrally the dorsal part of the intergeniculate nucleus is seen to be entirely atrophied. There is also a considerable degree of secondary

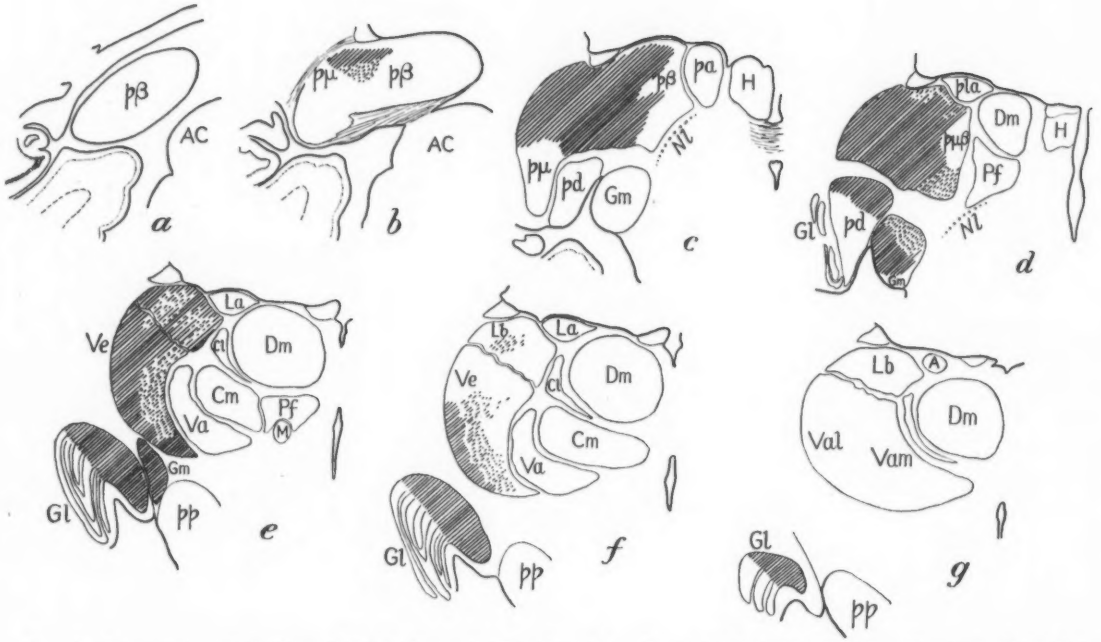

FIG. 2.—Transverse sections through the thalamus in Experiment A. In this and similar diagrams the areas of complete cell atrophy are indicated by hatching, while areas in which cell degeneration is partial are marked by interrupted lines.

degeneration affecting the medial geniculate body in most of its extent at this level, except at its medio-ventral angle. However, there are numerous scattered normal cells in the atrophied part of this nucleus (fig. 2*d*). A few sections more rostrally the whole of the medial geniculate body becomes almost completely atrophied except for a small group of cells at its ventral border. Here the whole transverse extent of the lateral geniculate body comes into view. The whole of its medial half is completely atrophied, a sharp line down the median axis of the nucleus separating the normal from the degenerated part. The degeneration of the medial half of the lateral geniculate body extends throughout its antero-posterior length.

At section 110, which cuts through the rostral pole of the medial geniculate body, the pars externa and the pars arcuata of the ventral nucleus become defined. The whole of the pars externa has at this level undergone complete cell atrophy except for scattered normal cells in its medial part. Similarly, almost all the cells of the nucleus lateralis *b* have disappeared except for a group of scattered cells in its central and dorsal part. Element *La* of the lateral nucleus remains intact and the cyto-architecture of the pars arcuata of the ventral nucleus also appears normal. There is no evidence of any secondary degeneration or gliosis in the dorso-medial, centre median, parafascicular or lateral central nuclei. The rostral pole of the medial geniculate body is completely atrophied (fig. 2*e*). A few sections further forwards (section 125) the normal cells at the medial border of the pars externa of the ventral nucleus form a much more conspicuous group, though their density is still less than normal. Normal cells also become more numerous in element *Lb*, especially at its dorso-lateral angle (nucleus angularis of Friedemann). At section 160 very little complete atrophy remains except for the medial half of the lateral geniculate body (fig. 2*f*). There is still considerable gliosis throughout the greater part of the pars externa of the ventral nucleus, and a zone of almost complete cell atrophy persists along its ventro-lateral margin. Further, in the middle of this element there is a partial atrophy. In nucleus *Lb* a slight degree of partial atrophy only is to be observed in its centre.

The first section of the third block cuts through the rostral pole of the lateral geniculate body, the medial half of which still shows complete degeneration. All the other elements of the thalamus at this level and further forwards are entirely normal in their cyto-architecture (fig. 2*g*).

In summarizing the results of this experiment, it may first be noted that the complete degeneration of the medial half of the lateral geniculate

body is evidently due to the extension of the lesion into the dorsal half of the area striata of the cortex and to its encroachment on the dorsal half of the optic radiations close to the lateral wall of the posterior horn of the lateral ventricle. The atrophy in the rostral part of the medial geniculate body is the result of the involvement of the caudal part of the auditory area within the lips of the Sylvian fissure, as well as of a portion of the auditory radiations. Almost the whole of that part of the pars externa of the ventral nucleus which receives the termination of the fillet system has undergone secondary degeneration, associated with the destruction by the lesion of the post-central gyrus. However, a zone of normal cells persists along the medial aspect of this thalamic element, and it is probable that this is due to the fact that the lesion did not extend so close to the central fissure at its lower end, leaving here a considerable part of the face area of the general sensory cortex. It is a noteworthy fact that the pars arcuata of the ventral nucleus seems to have escaped atrophy. Previous observations have shown that this element of the ventral nucleus projects on to the precental gyrus (Clark, 1936). The degeneration in the posterior part of nucleus *Lb* is probably related to the destruction of areas 5 or 7, or both, in the post-sensory parietal cortex (*see* Clark and Boggon, 1935).

The cell atrophy in the pulvinar must evidently be due to the involvement by the lesion of some other part of the parietal lobe, or the posterior end of the temporal lobe.

Experiment B.—O.M. 55. Operated March 27, 1936, killed May 6, 1936.

This experiment consisted in a local ablation of the posterior Sylvian receptive region defined by Poliak on the basis of Marchi studies. This region extends along the walls of the Sylvian sulcus from the auditory area to its posterior extremity. The extent of the lesion is shown in figs. 3 and 4. Rostrally it reaches to the level of the lower end of the central sulcus, 14 mm. behind the Sylvian point. Above it extends as far as the middle part of the intraparietal sulcus. Below and behind it involves the exposed surface of the superior temporal gyrus, the main lesion being limited by the upper lip of the parallel sulcus. The lesion is 12 mm. wide near its rostral extremity and 8·5 mm. wide near its posterior extremity. It is 26 mm. in length. The illustration shows that anteriorly it involves the lower end of the post-central gyrus (areas 1, 2 and 3). Transverse sections were taken through the length of the lesion. From these it is clear that the cortical injury was almost entirely confined to the immediate

boundaries of the Sylvian sulcus. However, there are two superficial abrasions of the exposed cortex below the caudal half of the parallel sulcus (in Areas 18 and 19) as well as two very small abrasions on the surface of the area striata behind the lunate sulcus (fig. 1). In addition, there is a slight involvement of the insular cortex in the Sylvian fossa.

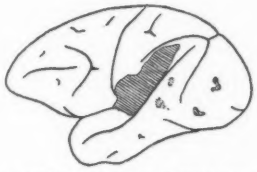

FIG. 3.—The cortical lesion in Experiment B. × ½.

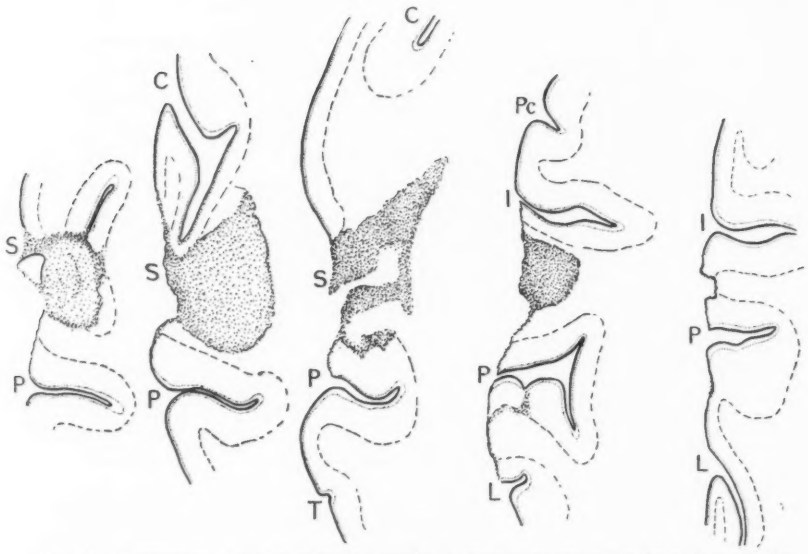

FIG. 4.—Transverse sections taken at regular intervals antero-posteriorly through the lesion in Experiment B. *C.*—Central sulcus. *I.*—Intraparietal sulcus. *L.*—Lunate sulcus. *P.*—Parallel sulcus. *Pc.*—Post-central sulcus. *S.*—Sylvian sulcus.

The thalamus.—Serial sections through the thalamus show considerable cell atrophy in its caudal part. The first sections of the first block cut through the tip of the pulvinar. Here the cyto-architecture of the pulvinar (element *pS*) is normal. Further forward, where the pulvinar becomes adherent to the side of the mid-brain, a patch of partial cell

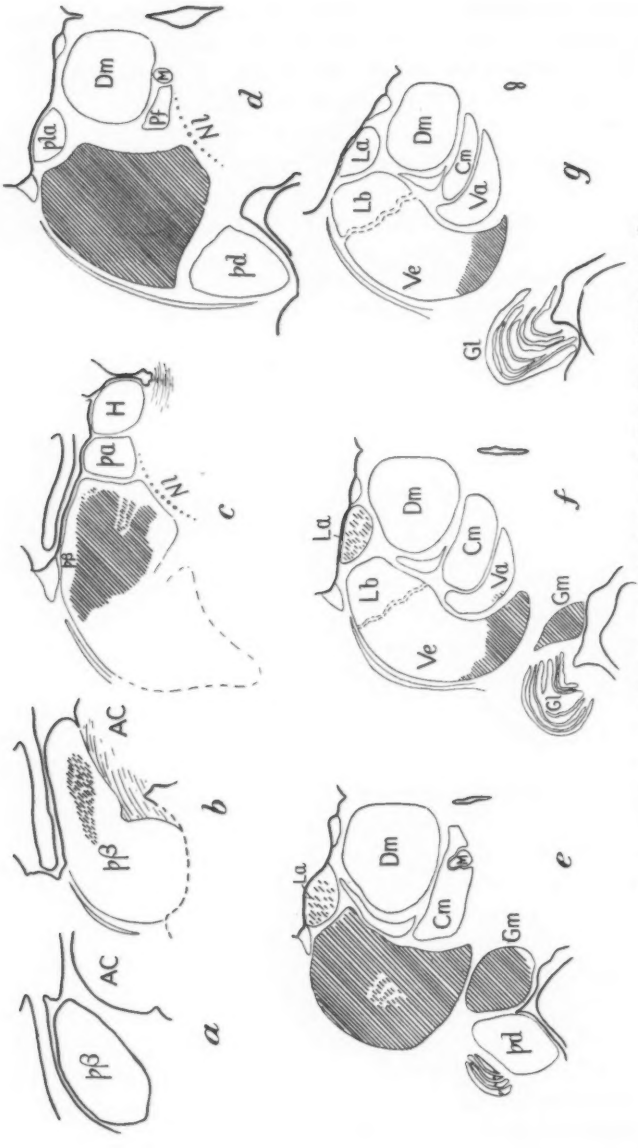

FIG. 5.—Transverse sections through the thalamus in Experiment B showing the areas of cell degeneration.

atrophy appears in its dorso-medial part extending laterally towards the centre (fig. 5*b*). In this area there is a conspicuous thinning out of the cells with an accompanying gliosis. For a number of sections this area of secondary degeneration remains fairly constant. By section 176, however, it has become quite large and extremely well defined. Here it extends over almost the whole of the dorsal half of the pulvinar involving the element $p\beta$. There remains a zone of normal cells at the dorsal surface, and element *pa* (at the side of the habenular nucleus) is quite unaffected. Ventral to the cortico-tectal fasciculi (which penetrate the pulvinar at this level) there is no sign of cell atrophy. In other words elements *pd* and $p\eta$ appear normal. Thus the area of atrophy is confined to element $p\beta$, and it is interesting to note the sharp contrast between this degenerated element and the other normal elements of the pulvinar. This area of atrophy preserves relatively the same extent to the end of the first block, which cuts through the habenular ganglion and the posterior commissure.

The first section of the second block cuts through the rostral part of the pulvinar and the caudal end of the dorso-medial nucleus (fig. 5*d*). At this level the pulvinar is completely atrophied except for elements *pd* and *pla*. The latter are entirely normal in their cyto-architecture. At section 42 the caudal ends of the geniculate bodies appear. The medial geniculate body is entirely atrophied throughout its antero-posterior extent except for a small group of normal cells at its ventro-medial angle. The lateral geniculate body shows a thin band of cell atrophy in its caudal third occupying the ventro-lateral segments of its laminæ. This slight degeneration is evidently the result of the small abrasion of the visual cortex already referred to. By section 80, odd normal cells begin to appear in the dorsal part of the atrophic area. Towards the rostral pole of the medial geniculate body, the elements of the ventral nucleus of the thalamus become evident (fig. 5*f*). Here cell degeneration is mainly confined to the ventral third approximately of the pars externa of the ventral nucleus, and the medial geniculate body. There is also quite distinct partial cell degeneration in element *La* of the lateral nucleus, especially in its ventral half. The pars arcuata of the ventral nucleus is entirely normal except only for a suggestion of partial atrophy in a small zone at the middle of its lateral border. The centre median and dorso-medial nuclei and the nucleus of the medial medullary lamina (nucleus centralis lateralis) are intact. As the sections are traced further forwards the area of cell atrophy in the pars externa of the ventral nucleus shrinks down to its ventro-medial angle.

The third block cuts through the middle of the lateral geniculate body and the rostral part of the centre median nucleus. Here the zone of cell atrophy is confined to the ventro-medial angle of the pars externa of the ventral nucleus. The pars arcuata and the centre median nucleus are normal, and, at this level, element *La* of the lateral nucleus also shows no cell degeneration. Rostral to the level of the centre median and arcuate nuclei, no more cell atrophy is evident.

Experiment C.—O.M. 157. Operated September 14, 1936, killed October 26, 1936.

This experiment involved the removal of the dorsal half of cortical areas 18 and 19 on the exposed surface of the brain. After death the lesion was found to measure 24 mm. in vertical diameter, reaching to within 6 mm. of the dorsal margin of the hemisphere above, and below almost to the extremity of the superior lunate sulcus. Rostrally it extends to the caudal lip of the parallel sulcus, and caudally it involves

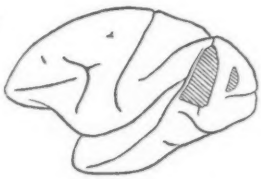

FIG. 6.—The cortical lesion in Experiment C. × ½.

the opercular lip of the striate area. In addition there was found to be a small superficial abrasion of the striate area near the upper half of the occipital pole (fig. 6 and Plate IV, fig. 2).

The thalamus.—Sections through the extreme pole of the pulvinar show a perfectly normal cyto-architecture. As the sections are traced forwards a small patch of gliosis and partial cell atrophy appears at the lateral margin of the pulvinar, involving here element *pη* of Friedemann (fig. 7*a*). This small area of degeneration remains relatively of the same size through a number of sections and is quite sharply localized. At the level at which the pulvinar becomes adherent to the side of the mid-brain (fig. 7*b*), the atrophic area is slightly more expanded, forming here a wedge-shaped patch extending into the ventral part of the pulvinar from its lateral margin. The main part of the pulvinar—element *pβ*, and other elements such as *pa* and *pla* are unaffected. Further rostrally, where the cortico-tectal fasciculi come into view cutting off element *pd* below from the rest of the pulvinar, the affected

cells form a sharply circumscribed area of total cell atrophy in the dorso-lateral quadrant of *pd* (fig. 7*c*). The caudal extremity of the lateral geniculate body shows a complete degeneration of its dorso-medial half, all layers being involved. At this level (fig. 7*d*) the atrophic area in the pulvinar is confined to a tiny patch in the dorsal angle of element *pd*. A few sections further forwards this area of degeneration has disappeared. At its maximum size in transverse section, the area of

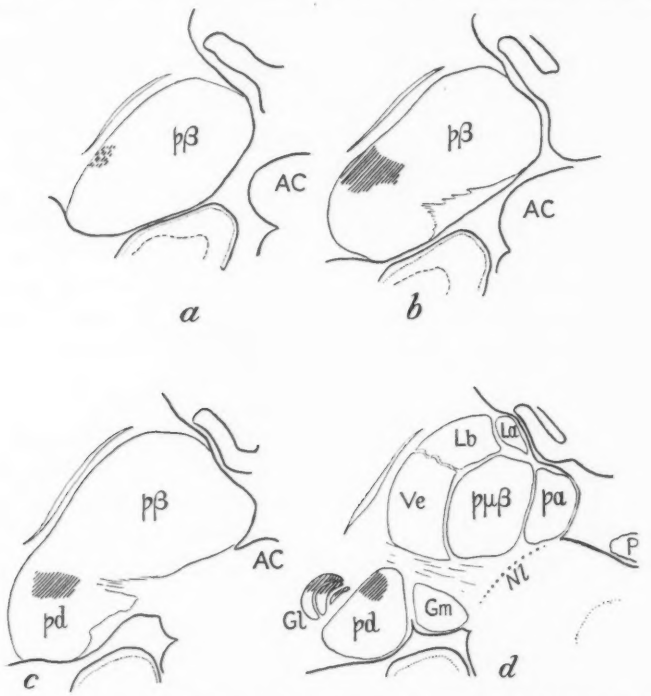

FIG. 7.—Transverse sections through the pulvinar in Experiment C, showing the areas of cell atrophy.

atrophy in the pulvinar measures 2·8 by 1·7 mm., while its antero-posterior diameter (extending over 120 sections) is estimated at 1·8 mm. In relation to the extent of the cortical lesion, the cell atrophy in the pulvinar is therefore quite restricted.

Experiment D.—O.M. 158. Operated September 15, 1936, killed October 27, 1936.

In this animal, the lower half of areas 18 and 19 on the exposed

surface of the cerebral hemisphere was excised. The extent of the lesion as seen after death is shown in fig. 8. It was found to measure

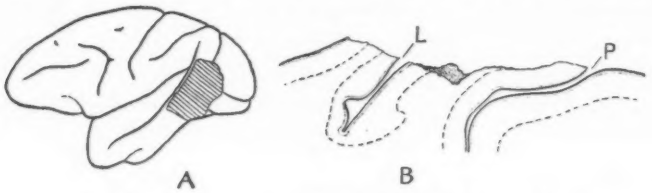

FIG. 8A.—The cortical lesion in Experiment D. × ½.

FIG. 8B.—Antero-posterior section through the middle of the lesion in Experiment D. × 2½. *L.*—Lunate Sulcus. *P.*—Parallel sulcus.

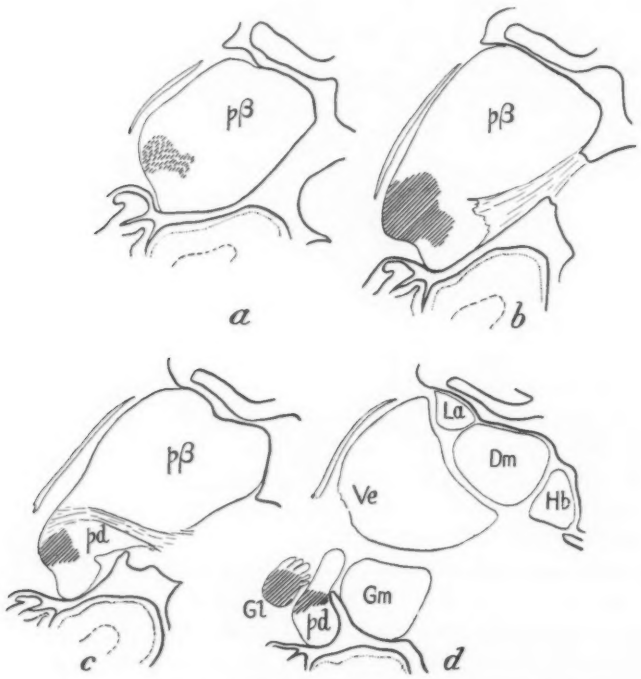

FIG. 9.—Transverse sections through the pulvinar in Experiment D, showing the areas of cell atrophy.

23 mm. in vertical and 17 mm. in antero-posterior diameter. Rostrally it reaches to the caudal lip of the parallel sulcus, and behind involves the opercular lip of the striate area. Above it extends to the upper end

of the Sylvian sulcus, 17 mm. from the dorsal margin of the hemisphere, and below to the lower margin of the hemisphere.

The thalamus.—The cyto-architecture at the extreme pole of the pulvinar is normal. Seventy sections in front of the tip of the pole, a small patch of gliosis and partial cell atrophy appears at the ventro-lateral angle of the pulvinar. This becomes more distinct a few sections further forwards, and extends somewhat medially (fig. 9*a*), and it soon forms a well-defined patch of almost complete cell atrophy confined to Friedemann's element *pη*. Where the cortico-tectal fasciculi come into view, the area of gliosis and cell atrophy is limited to that part of the pulvinar lying ventrally, i.e. in the lateral half of element *pd*. Beyond this level, the area diminishes in size, though remaining sharply circumscribed (fig. 9*c*). Further rostrally, the lateral geniculate body appears, showing complete atrophy of the cells in its ventro-lateral half. Here the degeneration in element *pd* is limited to a tiny patch near its centre, which disappears in a few sections. At its maximum development in cross-sectional area, the patch of cell atrophy in the pulvinar measures 2·8 mm. by 2·4 mm. Its antero-posterior extent, as estimated from the number of sections, is approximately 3·4 mm.

Discussion.

In Experiment A, the ablation of the whole of the exposed area of the parietal lobe of the cortex (including Poliak's posterior Sylvian receptive area) was followed by extensive cell atrophy in the main nuclear element of the pulvinar (*pβ*) except at its caudal pole, and in the dorsal half of the intergeniculate nucleus (element *pd*). Previous experiments (Clark and Boggon, 1935) have suggested that element *pd* projects on to the periparastriate areas (Brodmann's areas 18 and 19), while isolated lesions in the parietal cortex (not involving the posterior Sylvian receptive region) were not followed by atrophy in the main element, *pβ*, of the pulvinar. The results of Experiment A may therefore be taken to indicate that element *pβ* projects on to the posterior Sylvian receptive area. The second experiment of the present series was devised in order to test this conclusion. In this case, a cortical lesion limited to the Sylvian area was followed by cell atrophy in the main element of the pulvinar almost identical in its extent with that in Experiment A, while the intergeniculate nucleus remained intact. Thus it appears certain that the main element of the pulvinar projects on to the cortex forming the walls and lips of the Sylvian sulcus. Previous experiments have indicated that this

cortex extends forwards to become contiguous with the audito-sensory area of the superior temporal gyrus (Clark, 1936), for in two cases in which a relatively small lesion was made in this gyrus, cell atrophy in the medial geniculate body was accompanied by an area of degeneration in the main element of the pulvinar, *pβ*. In order to test the inference from Experiments A and B that the periparastriate areas receive fibres from element *pd* of the pulvinar, Experiments C and D were performed in which lesions were confined to the upper and lower halves approximately of these areas on the lateral surface of the hemisphere. In both these cases a well-marked area of cell atrophy was found in element *pd* of the pulvinar and in its caudal extension, element *pη*. Moreover, it appears that the upper and lower parts of these areas are related to the dorsal and ventral parts of *pd* respectively. On the other hand the main element of the pulvinar was unaffected. Thus it may be regarded as certain that areas 18 and 19 on the lateral surface of the brain receive fibres only from quite a limited portion of the pulvinar, i.e. elements *pd* and *pη*. It is extremely probable that this is also the case with the equivalent cortical areas on the medial surface of the brain. Walker (1936) has recently reported an experiment (Case 9, MY) in which a lesion was made involving most of area 18 and a considerable portion of area 19 on the lateral surface of a monkey's brain, and from his description it seems also that these areas on the medial surface were almost totally destroyed. The retrograde cell degeneration was more extensive than in either Experiment C or D of this paper, but it was apparently confined to elements *pd* and *pη* of the pulvinar. In spite of this, Walker, in his general summary, suggests that the whole of the pulvinar projects on to areas 18 and 19. That this is not the case is rendered certain by the present observations. In a paper dealing with the cerebral representation of the retina in the chimpanzee, Poliak and Hayashi (1936) note that, following a lesion involving areas 18 and 19 of the cortex in this animal, there was marked partial degeneration in the pulvinar, but they do not state its localization. In an experiment reported elsewhere (Clark, 1936), a lesion involving the rostral extension of areas 18 and 19 on the lateral aspect of the hemisphere led to no secondary degeneration in the thalamus. The sections of the thalamus of this case (O.M. 87) have since been re-examined, confirming the observation that the cyto-architecture of the pulvinar appears to be quite unaffected. Thus it seems probable that element *pd* projects, at least mainly, on to that region of the cortex which is immediately

adjacent to the striate area—possibly to area 18 only. It may be inferred, further, that the two cortical areas which receive fibres from the pulvinar are separated by a zone of cortex which is not related to the thalamus by ascending connections. It may be noted that in these experiments no cell degeneration was present in the extreme caudal pole of the pulvinar, or in the well-defined element *pa* (which lies alongside the habenular nucleus).

The conclusion that two separate portions of the pulvinar are related by thalamo-cortical fibres to two different areas of the cortex raises the question of the nature of the impulses which they are concerned with transmitting. This must remain unsettled until something is known of the ascending connections of the pulvinar from lower levels. Internuclear connections between the pulvinar and the lateral geniculate body have been described by several authors on the basis of normal Weigert preparations, but the uncertainty of this type of evidence allows of no positive conclusions. The fact that the cells of the lateral geniculate body all degenerate after destruction of the striate cortex suggests that in fact this body is entirely concerned with cortical projection. Brouwer (1923) has shown on the basis of Marchi studies (and his work has since been confirmed) that optic tract fibres almost certainly do not terminate in the pulvinar, and a recent study of the termination of ascending tracts from the spinal cord and brain-stem (Clark, 1936) failed to show that any fibres from these sources reach it.

Conclusions.

Experimental study of secondary degeneration following cortical lesions indicates that the pulvinar, in regard to its cortical projection, can be divided into two parts. The line of separation between them is marked out approximately by the bundle of cortico-tectal fibres which penetrates the pulvinar to reach the mid-brain. Element *pd* (with its caudo-lateral extension *pη*), which lies in close topographical relation to the lateral geniculate body, projects on to that part of the peri-parastriate area which lies immediately adjacent to the visual cortex. The main element of the pulvinar, *pβ*, projects on to the posterior Sylvian receptive region which was originally defined by Poliak on the basis of Marchi studies. This region extends forwards along the Sylvian fissure to become contiguous with the auditory projection area of the medial geniculate body in the superior temporal gyrus.

The cost of the animals used in this research was met by a grant from the Royal Society, which we wish gratefully to acknowledge.

ABBREVIATIONS.

A.	Anterior nucleus.
AC.	Anterior colliculus.
Cl.	Nucleus centralis lateralis.
Cm.	Centre median nucleus.
Dm.	Dorso-medial nucleus.
Gl.	Lateral geniculate body.
Gm.	Medial geniculate body.
H.	Habenular nucleus.
La., *Lb.*	Elements of the lateral nucleus.
M.	Meynert's bundle.
Nl.	Nucleus limitans.
Pf.	Parafascicular nucleus.
pa., *pβ.*, *pd.*, *pla.*, *pα.*, *pαβ.*	Nuclear elements of the pulvinar.
pp.	Pes pedunculi.
Va.	Pars arcuata of the ventral nucleus.
Val.	Pars antero-lateralis of the ventral nucleus.
Vam.	Pars antero-medialis of the ventral nucleus.
Ve.	Pars externa of the ventral nucleus.

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Notices of Recent Publications.

Handbuch der Neurologie, Herausgegeben von O. Bumke und O. Foerster. Berlin: Julius Springer.

The latest volumes of this System of Neurology to appear attain the same high standard as their predecessors and confirm the earlier impression that the whole system is essential to the neurologist who would keep up to date in his profession. The comprehensive bibliographies at the end of every chapter are a particularly valuable supplement to the full and authoritative treatment of each subject.

Band VI. *Grosshirn, Vegetatives Nervensystem, Körperbau und Konstitution.* S. 1153, mit 549 Abbildungen. Price RM. 223.

This valuable and excellent volume presents an extremely interesting study of the functions and pathology of the brain, for the two last sections, on the vegetative system and constitution, occupy only a relatively small part of it. In the first 450 pages Foerster deals with the cerebral systems of motion and sensation. In each of these chapters he first describes the anatomical structures which underlie these functions, and then deals with the results of their electrical stimulation in the human brain, a subject in which his experiences are unrivalled. It is already known that the "motor areas" of the cortex which he defines are much more extensive than they are generally accepted to be; any area from which he has been able to elicit a motor response is regarded as "motor." The effects of both irritative and destructive lesions are then considered, and the numerous clinical types produced by cortical lesions are fully described. The analysis and descriptions of symptoms of disease, and especially of motor syndromes, are as striking a contribution to the subject as his electrical experiments, but it must be said that his observations diverge considerably in many points from those of others who have studied these problems.

Brouwer writes more concisely but exhaustively on the visual system, and Pfeifer on the auditory radiations and the cortical centre for hearing, touching also on its relation to aphasia and amnesia. The separate chapter on aphasia has been undertaken by Isserlin; every aspect of this important subject, the physiological, anatomical and psychological, are adequately dealt with and the whole is characterized by its clear and critical treatment. The agnosias and apraxia are fully discussed at considerable length from every point of view by J. Lange. Bostroem contributes a short but excellent chapter on the mental symptoms of cerebral disease. In his article on the vegetative system Frank

deals with such symptoms as fever, metabolic disturbances and essential hypertension, as well as with those disorders generally attributed to its disease. In the last chapter Kretschmer summarizes his views on the significance of build and on constitution.

Band VII. *2ter Teil. Liquor, Hirnpunktion, Röntgenologie.* S. 553, mit 416 Abbildungen. Price RM. 117.

The second part of the seventh volume is devoted to special methods of diagnosis. In a concisely written but comprehensive article L. Guttmann deals with the anatomy, physiology and mechanics of the cerebrospinal fluid, and includes a critical review of the many debatable questions on its mechanics and pathological variations. Neisser and Forster contribute a short chapter on puncture of the brain for diagnostic purposes. Stenvers writes on ordinary radiological diagnosis, and Guttmann on encephalography and myelography by the use of "contrast" substances, as air, iodine, thorotrast, &c., and on arteriography. In both of these chapters, which are liberally illustrated, the technique of operation and the interpretation of the films are fully described.

Band XI. *Traumatische, Präsenile und Senile Erkrankungen und Zirkulationsstörungen.* S. 548, mit 148 Abbildungen. Price RM. 104.

Marburg opens this volume with a long and valuable article on the traumatic affections of the brain and spinal cord, in which he discusses the origin and nature of cerebral concussion as well as the grosser lesions which result from mechanical injuries. He describes the symptomatology of epidural and subdural hæmorrhages, traumatic softening and œdema, and discusses post-traumatic epilepsy. In addition to mechanical injuries of the spinal cord he deals with those resulting from electrical accidents, and with the relation of trauma to later developing organic disease.

The greater part of the volume is, however, occupied by Hiller's chapter on circulatory disturbances of the brain and spinal cord, in which, in addition to the symptoms of gross vascular lesions, the effects of arteriosclerosis and of disordered circulation on nervous tissue are fully considered. Grünthal contributes a short but excellent chapter on the senile and presenile affections of the brain and spinal cord, including senile dementia and Pick's and Alzheimer's diseases.

Band XIV. *Raumbeengende Prozesse.* S. 417, mit 280 Abbildungen. Price RM. 86.

This volume is wholly devoted to tumours of the central nervous system. Antoni of Stockholm contributes an article on tumours of the spinal cord and its membranes, in which the pathology of the various forms of growth which

involve these parts is particularly fully described and well illustrated, but the symptoms they cause and their diagnosis are also adequately discussed. One half of McLean's (of Portland) chapter on intracranial tumours is devoted to their histology, but this is so concisely and clearly written that it will be welcome to clinicians. The incidence of each type of tumour, its clinical course, operability and radio-sensitivity are important features to which the author gives adequate attention. He discusses fully the nature and significance of the symptoms of increased pressure, but the space allotted to local diagnosis is insufficient. The employment of X-rays and other means of diagnosis is again introduced, and there is a short section on operative treatment. McLean has also written on pituitary tumours, including stalk tumours.

The invasion of the central nervous system by animal parasites as cysticercus, echinococcus, distoma, schistosoma and trichina, are fully dealt with by Henneberg, and Wartenberg discusses abscesses of the brain and spinal cord.

Die Bioelektrischen Erscheinungen der Hirnrindenfelder. von A. E. Kornmüller. Leipzig: G. Thieme. S. 118. Price RM. 7.80.

This monograph gives a valuable summary of the author's work on the electrical activity of the cortex, carried out during the past five years at the Kaiser Wilhelm Institute. It deals particularly with the localization of different types of activity, spontaneous or due to sensory stimuli, in areas of different cyto-architecture. In the monkey's cortex, for instance, not only is the response to illuminating the eye confined to the striate area, but there is an abrupt change in the frequency of the spontaneous oscillations in passing from it to the adjacent area 18. Most of the book deals with the brains of rabbits and apes, but there is a short chapter discussing Berger's work on man.

The author is a pioneer in this new method of research on the brain and his book shows what great possibilities it offers for further advance.

Neurological Surgery. By Loyal Davis. London: Henry Kimpton. 1936. Pp. 429, with 172 illustrations. Price 28s.

Dr. Loyal Davis has succeeded in compressing into a relatively small book the whole of neurological surgery—brain, spinal cord, peripheral nerves, and sympathetic nervous system. Comprehensive description of any particular lesion could not be expected, but the text seems to be adequate. The book is addressed to the general practitioner and not to the highly experienced clinician or surgeon, but because it is a personal record, and because Dr. Davis has had extensive experiences in experimental surgery and physiology, there is much of interest. In illustration of the scope of the book the point may be made that only 81 pages are devoted to intracranial tumours, and that whereas seven lines are devoted to colloid cysts of the 3rd ventricle, several pages are devoted to the problem of sympathetic afferents in the perception of pain. Probably

the average general practitioner is not particularly interested in either subject but both can be made fascinating, and on the one he has chosen Dr. Davis writes authoritatively and will be read with interest. A similar bias can be discovered elsewhere and would be more remarkable, maybe, if it were absent. A man writes best about that which he best knows. The illustrations are good and descriptions of operative steps have been reduced, very sensibly, to a minimum.

Course of Changes in the Spinal Fluid of Syphilitics. By ESBERN LOMHOLT. *Acta psychiatrica et Neurologica*, Supplementum XI. Copenhagen: Levin and Munksgaard. 1936. Pp. 96.

Since 1920 compulsory notification of syphilis has existed in Denmark, and a careful record has been kept of the subsequent medical history of all syphilitics. These records have enabled the author to trace the course of the disease in a very large number of patients on whom one or more lumbar punctures had been carried out in the early stages. It has thus been possible to assess the prognostic significance of the meningeal reactions which occur in the secondary stage of the disease. This problem has been attacked from two points of view: (1) What proportion of syphilitics develop neurosyphilis? and (2) what were the findings on lumbar puncture in the early stages of the disease in patients who subsequently develop neurosyphilis? From an examination of the available records he finds that while most of the meningeal reactions of the secondary period are ephemeral and without prognostic significance those reactions which persist into the latent period are not so favourable. Thus he could find no case in Denmark, and only one certain case in the literature, in which neurosyphilis developed after the cerebrospinal fluid had been found normal during the latent period. This confirms the experience of Ravaut who found that neurosyphilis is most likely to develop in cases in which the meningeal reactions of the secondary stage do not yield to treatment. Lomholt also found that general paralysis seldom appeared in patients who had received abortive treatment during the primary stage and in whom no secondary exanthem had appeared. But cases in which the spinal fluid was already abnormal during the primary stage might develop general paralysis without passing through a secondary stage. When such far-reaching conclusions are arrived at documentary evidence has a special value, and this evidence is provided in the series of tables and case histories which form the second half of the book.

While the prognostic significance of early changes in the cerebrospinal fluid in syphilis is the most important question dealt with in this monograph, many subsidiary points are raised, and to some of these the author has been able to give fairly definite answers. The Danish records of syphilis are unique and we are therefore specially grateful to Dr. Lomholt for making his analyses of these records available to all.

La Douleur dans les Affections du Système Nerveux Central. Par JULIAN DE AJURIAGUERRA. Paris: G. Doin. Fr. 25.

The time was ripe for the preparation of a monograph dealing with the pathophysiology and clinical analysis of central pain. This difficult subject has been ably approached in Ajuriaguerra's study. Critics may point out that the superstructure of hypothesis balances somewhat precariously on a too slender erection of established data, but this is partly inherent in the nature of the subject-matter. Ajuriaguerra's conclusions probably will not receive universal acceptance, but his arguments and opinions are thoughtful and merit consideration. His clinical material is particularly rich, though many will argue that in dealing with spinal cases of central pain, he has cast his net rather too wide. No reference is made to central pains following herpes zoster, and the author does not refer to psychogenic pains at all fully in discussing diagnosis or pathogenesis.

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EDITOR.